Influenza Antivirals for Pandemic H1N1: Overview

22 February, 2010

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and
Wellcome Trust, London, UK

Conflict of Interest Declarations- FG Hayden

• No financial COI since 2006
• Unpaid adviser (sometimes with access to confidential information) for Abbott, Adamas, Allos, Biocryst, Crucell, Nexbio, GSK, Inhibikase, Kirin, Respivert, Roche, Toyama, 3V Biosciences, Vaxinnate since 2008

Table R3: Use of antivirals for treatment of influenza

<table>
<thead>
<tr>
<th>Population</th>
<th>Pandemic (H1N1) influenza since 2009</th>
<th>Multilayer co-circulating influenza A subtypes or viruses with different antiviral susceptibilities</th>
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<td>Mild to moderate uncomplicated clinical presentation</td>
<td>Oseltamivir or zanamivir (IN)</td>
<td>Zanamivir, oseltamivir plus M2 inhibitor (IN)</td>
<td>Oseltamivir or zanamivir</td>
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<td>Otherwise</td>
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</table>

a Incubation period: 1-3 days; latency: 2-4 days; usually 1-3 days (range: 2-7 days), vomiting, nausea, myalgia, fatigue, headache; cough, fever, cough, running nose, muscle pain; may develop complications such as bacterial pneumonia or bacterial sinusitis, otitis media, and bronchitis with exacerbation related to abnormalities of the immune system, COPD, chronic lung disease or diabetes. Infection should not be confused with post-vaccination syndrome (R5).

b Suspected seasonally influenza A viruses only (e.g., H1N1, H3N2, H5N1, H7N9). Severe cases should be treated with antiviral prophylaxis for 48 hours after exposure.

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WHO Guidelines for Pharmacological Management of Pandemic (H1N1) 2009 Influenza and other Influenza Viruses, August 09
Antivirals for Pandemic H1N1: Outline

- Therapeutic effectiveness of current agents
  - Pandemic H1N1
  - Hospitalized seasonal influenza patients
  - H5N1 illness
- Antiviral resistance (H275Y in N1)
- New antiviral agents and approaches
  - Clinical development candidates
  - Combinations

Activity of Neuraminidase Inhibitors and T=705 against Pandemic H1N1 Virus in Mice

- Treatments initiated at 1 hr post infection

Itoh et al. Nature published online 2009

Oseltamivir Treatment of Pandemic H1N1 Illness, Vietnam, May - July 2009

- 292 pandemic H1N1 rRT-PCR positive patients
  - Oseltamivir (75 mg bid in adults) until negative
    - All mild illness, 1 with infiltrates
  - Viral RNA detection from URT in 14% on day 5 and longer in 7% (up to day 12-14)
    - All culture negative after day 5
  - Oseltamivir susceptibility testing
    - 3 who were RNA+ > 5 days had resistant virus with H275Y mutation on days 5, 6, and 11.

Hien TT et al. ProMED 8 August 2009 and 11 October 09
Risk Factors for Prolonged Pandemic H1N1 RNA Detection

- 350 pts with mild-moderate illness
- Early oseltamivir therapy was key variable.

Cao et al. NEJM 2009

Detection of Infectious Pandemic H1N1 Virus

- 53 adults aged 17-24 yrs with pH1N1 illness
- Median duration of illness = 5.6 days (1-11)
- Isolation of pH1N1 virus > 5 days and after Sx resolution.


Nasopharyngeal pH1N1 Viral RNA Levels in Hospitalized Patients Given Oseltamivir

- Slower decline in viral shedding was observed in all severe patients compared to mild disease.

To et al. CID 50: , 15 March 2010
Antiviral Use in Pandemic H1N1 Hospitalizations, April - June 2009, USA

<table>
<thead>
<tr>
<th>Patient group</th>
<th>No. with data</th>
<th>Percent treated*</th>
<th>Median days from illness onset (range)</th>
<th>Percent treated &lt; 48 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalized</td>
<td>268</td>
<td>75%</td>
<td>3 (0 to 29)</td>
<td>39%</td>
</tr>
<tr>
<td>ICU admission</td>
<td>65</td>
<td>86%</td>
<td>6 (0 to 24)</td>
<td>23%</td>
</tr>
<tr>
<td>Fatal case</td>
<td>19</td>
<td>90%</td>
<td>8 (3 to 20)</td>
<td>0</td>
</tr>
</tbody>
</table>

*188 oseltamivir, 19 zanamivir; 27 oseltamivir + adamantane
Jain et al. NEJM, published 8 October 2009

Days of Illness to Treatment and Outcomes, Manitoba, April – September 2009 (N = 795)

Oseltamivir Treatment in Hospitalized Patients with Season Influenza

<table>
<thead>
<tr>
<th>Location, Seasons</th>
<th>Patients</th>
<th>% Fatal Cases</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toronto, 2005-06</td>
<td>Adults</td>
<td>Oseltamivir: 3.9% (4/103)</td>
<td>No Oseltamivir: 10.1% (22/219)</td>
</tr>
<tr>
<td>Thailand, 2004-06</td>
<td>Adults + Children</td>
<td>Oseltamivir: 1.6% (5/318)</td>
<td>No Oseltamivir: 13.0% (17/131)</td>
</tr>
<tr>
<td>Hong Kong, 2004-05</td>
<td>Adults</td>
<td>Oseltamivir: 2.2%* (5/232)</td>
<td>No Oseltamivir: 5.6%** (7/124)</td>
</tr>
</tbody>
</table>

* Oseltamivir ≤ 96 hrs after illness onset
** No oseltamivir or treated >96 hrs after onset

McGrew et al. CID 405:1568, 2007
Hanshaoworakul et al. PLOS ONE 4:e6051, 2009
Lee et al. CID 46:1323, 2008

Case Fatality Rate by Time From Symptom Onset to Treatment With Oseltamivir

Toovey et al. ICAAC 2009

Enteric absorption and pharmacokinetics of oseltamivir in critically ill patients with pandemic (H1N1) influenza


• 41 critically ill adults with suspected or confirmed pH1N1 who were admitted for ventilatory support
  – Plasma oseltamivir levels before gastric administration of the drug and at 2, 4, 6, 9 and 12 hrs after the fourth or later dose.
• Oseltamivir was well absorbed enterically, and dosage of 75 mg twice daily achieved plasma levels that were comparable to those in ambulatory pts.
**Characteristics of Antiviral Resistant Human Influenza Viruses - February 2010**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Seasonal A(H3N2)</th>
<th>Seasonal A(H1N1)</th>
<th>Pandemic A(H1N1)</th>
<th>Avian A(H5N1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance (mutation)</td>
<td>M2I (S31N)</td>
<td>Oseltamivir (H275Y)</td>
<td>M2I (S31N)</td>
<td>M2I (S31N)*</td>
</tr>
<tr>
<td>Efficient H2H transmission</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Virulence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Genetic stability</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Competes with wild type</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Varies by clade.

**Influenza Antiviral Resistance, 2008-2009: General Comments**

- In vitro resistance to M2Is (S31N) or oseltamivir (H275Y in N1) is high-level and confers clinical resistance (i.e., lack of in vivo effectiveness).
- M2I cross-resistance to entire M2I class, whereas NAI resistance is drug, influenza virus, and mutation specific.
  - Zanamivir inhibitory for N1 viruses with H275Y
- Recent resistant variants show no obvious reductions in virulence or transmissibility.
  - Outbreaks in healthcare facilities
  - Severe, sometimes fatal illness in at-risk patients

**Oseltamivir Resistance in Pandemic H1N1**

- Most sporadic, geographically dispersed detections
  - Clusters but no sustained community spread to date
  - 190 among >15,000 tested to 6 Jan 2010
  - All with H275Y mutation; no reassortment with seasonal H1N1
- Treatment - especially in immunocompromised hosts receiving prolonged therapy
- Those failing PEP (75 mg once daily)
- Non-drug recipients
- Most mild, self-limited illnesses
  - Except children and immunocompromised hosts
Oseltamivir Resistance in Pandemic H1N1, WHO Reports to 17 Feb 2010 (N=248)

IV Zanamivir for Oseltamivir-Resistant Pandemic H1N1 in Immunocompromised Host

• 10 yo girl with ALL and pH1N1 positive URI → diffuse pneumonia and mechanical ventilation → recovery
  Gaur et al. NEJM, published online 23 December 2009

Oseltamivir-Resistant Pandemic H1N1 Cluster, Vietnam, July 2009

• Cluster of 7 oseltamivir-resistant pH1N1 cases (all H275Y) linked to a 42-hr train journey in July
  – 6/10 seated in same carriage had RT-PCR+ illness (2 others non-symptomatic; 2 no follow-up).
  – 1 with RT-PCR+ illness in another carriage
  – No prior oseltamivir or exposure, but all 7 given oseltamivir Rx for illness
  • Most viral RNA negative by day 6 of illness
    – One positive to day 9 of illness with H257Y
  Mai et al. NEJM, published 7 January 2010
Clusters of Oseltamivir-Resistant Pandemic H1N1 in Immunocompromised Hosts

- Duke University Hospital, Oct - Nov 2009
  - 4 adults aged 43 - 67 years, all severely immunocompromised status; 3 fatalities
  - Same ward with illness onsets in a 2-week period
  - H275Y mutation identified in 3 before oseltamivir Rx
- University Hospital of Wales, Cardiff, Nov 2009
  - 8 patients with underlying haematological malignancies; no fatalities
  - H275Y treatment-induced in 2 cases
  - At least 4 patients contracted the resistant virus through person-to-person transmission.

Oseltamivir Antiviral Resistance: Comments

- Oseltamivir-resistant pandemic H1N1 2009 viruses are transmissible and can replicate and cause illness in healthy people in the absence of selective drug pressure.
  - Capable of causing severe illness and fatalities in high risk patients, especially immunocompromised hosts
- Dual M2 and NAI resistance in some pH1N1 isolates
  - If suspected or proven oseltamivir resistance, zanamivir is drug of choice
  - Inhaled zanamivir (Relenza) for PEP or early therapy
  - Intravenous zanamivir for serious illness

Investigational Anti-Influenza Agents

- NA inhibitors (NAIs)
  - Peramivir (IV)
  - Zanamivir (IV)
  - A-315675 (oral)
- Long-acting NAIs (LANIs)
  - C58958/R-118958 (topical)
  - Flunet® (topical)
- Conjugated sialidase
  - DAS181 (topical)
- Protease inhibitors
- Cationic airway lining modulators (ICALM)
- HA inhibitors
  - Cyanovirin-N
  - Sialyl-glycopolymer
  - Arbidol (oral)
- Polymerase inhibitors
  - Ribavirin (oral, IV, inhaled)
  - Viramidine (oral)
  - siRNA (IV, inhaled)
  - T-705 (oral)
- Antibodies (anti-HA, NA, M2)
- Interferons
### Selected Investigational Anti-Influenza Agents in Clinical Development - January 2010

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Sponsor</th>
<th>Route</th>
<th>Development phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zanamivir</td>
<td>NA</td>
<td>GSK</td>
<td>IV</td>
<td>Phase 2 + eIND</td>
</tr>
<tr>
<td>Peramivir</td>
<td>NA</td>
<td>Biocryst, Shionogi</td>
<td>IV</td>
<td>Phase 3 + EUA (licensed Japan)</td>
</tr>
<tr>
<td>Laninamivir (CS-8958)</td>
<td>NA</td>
<td>Biota, Daiichi-Sankyo</td>
<td>Inhaled</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Favipiravir (T-705)</td>
<td>NA</td>
<td>Toyama</td>
<td>Oral</td>
<td>Phase 2 → 3</td>
</tr>
<tr>
<td>DAS181</td>
<td>HA receptor</td>
<td>Nexbio</td>
<td>Inhaled</td>
<td>Phase 1 → 2</td>
</tr>
</tbody>
</table>

### Comparative Pharmacology of Neuraminidase Inhibitors in Adults

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Cmax (ng/ml)</th>
<th>Cmin (ng/ml)</th>
<th>Plasma T1/2 (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oseltamivir</td>
<td>PO</td>
<td>150 mg q 12 hr</td>
<td>~380-600</td>
<td>~280</td>
<td>6-10</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>IV</td>
<td>600 mg q 12 hr</td>
<td>32-30,700</td>
<td>340-400</td>
<td>1.5-2</td>
</tr>
<tr>
<td>Peramivir</td>
<td>IV</td>
<td>600 mg</td>
<td>~43,800</td>
<td>~70</td>
<td>8-21</td>
</tr>
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### NA Inhibitor Resistance Profiles

<table>
<thead>
<tr>
<th>NA mutation</th>
<th>NA type/subtype</th>
<th>Susceptibility in the NAI assay (fold Δ)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oselt</td>
<td>Zana</td>
</tr>
<tr>
<td>E119V</td>
<td>A/N2</td>
<td>R (&gt;50)</td>
</tr>
<tr>
<td>R292K</td>
<td>A/N2</td>
<td>R (&gt;1000)</td>
</tr>
<tr>
<td>H275Y</td>
<td>A/N1</td>
<td>R (&gt;300)</td>
</tr>
<tr>
<td>D198N</td>
<td>B</td>
<td>R (9)</td>
</tr>
</tbody>
</table>


*IC50 value - oseltamivir and zanamivir in 1 study
Summary of Recent Antiviral Clinical Trials

- Uncomplicated influenza
  - Peramivir: single IV dose (300 or 600 mg) superior to placebo and comparable to 5 days of oseltamivir in adults
  - Laninamivir (CS-8958): single inhaled doses of 20 mg or 40 mg comparable to 5 days of oseltamivir in adults and children
  - Favipiravir (T-705): higher doses comparable to oseltamivir in adults
- Hospitalized adults
  - Peramivir: multiple IV doses comparable to oseltamivir in hospitalized adults (phase 2)

Combinations Evaluated in Animal Models

<table>
<thead>
<tr>
<th>Combinations Evaluated in Animal Models</th>
<th>Combinations Tested or Under Evaluation in Humans</th>
<th>Future Considerations for Use in Combinations</th>
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<tbody>
<tr>
<td>Amantadine + ribavirin</td>
<td>Amantadine + oseltamivir</td>
<td>Other NAI (peramivir, laninamivir)</td>
</tr>
<tr>
<td>Amantadine + oseltamivir</td>
<td>Oral rimantadine + nebulized zanamivir</td>
<td>Polymerase inhibitor (favipiravir)</td>
</tr>
<tr>
<td>Rimantadine + oseltamivir</td>
<td>Oseltamivir + zanamivir</td>
<td>Sialidase inhibitor (DAS181)</td>
</tr>
<tr>
<td>Oseltamivir + ribavirin</td>
<td>Oseltamivir + T-705*</td>
<td>Antibody therapies</td>
</tr>
<tr>
<td>Oseltamivir + T-705</td>
<td>Amantadine + ribavirin + oseltamivir</td>
<td>Interferons</td>
</tr>
<tr>
<td>Amantadine + interferon + thymosin alpha</td>
<td>Amantadine + oseltamivir</td>
<td>Immunomodulators</td>
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* Pharmacokinetic and safety study only

Combination Antiviral Therapies in Influenza

- If virus M2 inhibitor susceptible, then synergistic interactions in vitro and ↑ survival in mice when combined with oseltamivir or ribavirin.
- If virus M2 inhibitor resistant, no benefit to use in combination with oseltamivir or ribavirin.
- Oseltamivir and ribavirin show primarily additive interactions in vitro and in murine model.

Effects of Double Combinations of Amantadine, Oseltamivir, and Ribavirin on Influenza A (H5N1) Virus Infections in Cell Culture and in Mice

Donald F. Sinco, Brett E. Harst, Min-Hai Wang, Kevin W. Bailey, and John D. Mercurio

Institute for Animal Research, Department of Animal, Feed and Commerce Science, Ohio State University, Columbus, Ohio
T-705 and NAI Combinations In Vitro

- In mice the oral combination of T-705 and oseltamivir showed dose-related additive to synergistic survival benefits for H1N1, H3N2, and H5N1 viruses
  
  Smee et al. Antiviral Res 83:A37, 2009

Meta-Analysis: Convalescent Blood Products for Spanish Influenza Pneumonia: A Future H5N1 Treatment?

- Literature review for reports of using convalescent blood products in treating pneumonia patients hospitalized in 1918-20
  - 8 studies; total of 336 treated patients
  - 1,219 controls received supportive care
  - None blinded, randomized, or placebo-controlled

- Overall mortality reduced from 37% to 16% (difference 21%, 95% CI, 15% - 27%).
  - Benefit if treated < 4 days after pneumonia Dx

Panel of 13 moAbs recovered from combinatorial display libraries
- Binding to hydrophobic pocket region in the stem domain of different HA subtypes within H1 and H9 clades


Heterosubtypic Neutralizing Monoclonal Antibodies Cross-Protective against H5N1 and H1N1 Recovered from Human IgM Memory B Cells
Anti-Influenza Activity of Human MoAb CR6261 in Mice

- Dose-related prophylactic effect against lethal challenge
- Therapeutic effect up to 4 days p.i.


Influenza A Virus Host Cell Interactions


NIAID Influenza Antiviral Development Workshop: New Generation

Division of Microbiology and Infectious Diseases (DMID),
National Institutes of Allergy and Infectious Diseases (NIAID),
National Institutes of Health (NIH),
Department of Health and Human Services (DHHS)
and Biomedical Advanced Research and Development Authority (BARDA),
Office of the Assistant Secretary for Preparedness and Response, DHHS
Natcher Building, NIH Campus
Bethesda, Maryland 20892

March 26-27, 2009
Antivirals for Pandemic H1N1 Influenza

- Resistance to adamantanes but susceptibility to multiple NAIs + investigational drugs
  - Sporadic isolates resistant to oseltamivir (H275Y)
- Delayed time to treatment observed in severe and fatal illnesses
- Antiviral therapy especially important for:
  - Patients with progressive illness or pneumonia
  - Patients with underlying medical conditions
  - Pregnant patients
- Important progress in development of IV therapies, agents with novel actions, and combinations