Antiviral Treatment and Chemoprophylaxis of Pandemic Influenza A (H1N1) Virus

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www.pandemicflu.gov  www.cdc.gov/flu
Antiviral Medications for Influenza

- Two classes (Adamantanes, Neuraminidase Inhibitors)
  - Monotherapy for treatment or chemoprophylaxis
  - Interfere with virus replication

- Differences in approved age groups, adverse effects, contraindications, routes of administration, metabolism, antiviral resistance, cost, availability
Adamantanes: Amantadine, Rimantadine

- Activity against influenza A viruses only
  - Orally administered (liquid, tablet)
  - Adverse effects: Gastrointestinal, CNS

- Treatment or chemoprophylaxis of influenza A in persons aged ≥1 year

- Resistance can develop rapidly during treatment of susceptible strains (10-30%), cross-resistance

- Pandemic H1N1 virus is resistant to Amantadine and Rimantadine
Neuraminidase Inhibitors
Oseltamivir (Tamiflu), Zanamivir (Relenza)

- Activity against influenza A and B viruses

- **Oseltamivir**: Oral administration (liquid, capsule)
  - Treatment or chemoprophylaxis of ≥1 year*
  - Adverse effects: Gastrointestinal, rare CNS sx. (adolescents)

- **Zanamivir**: Orally inhaled powder (disk inhaler)
  - Approved for treatment of ≥7 years
  - Approved for chemoprophylaxis of ≥5 years
  - Adverse effects: Bronchospasm, rare CNS sx.
    - Contraindicated in persons with chronic pulmonary disease, asthma

*Approval for use in children aged <1 year; emergency use (U.S.)
Oseltamivir, Zanamivir
Treatment Efficacy - Seasonal Influenza

- Efficacy of early treatment (<48 hours of onset) of uncomplicated illness (adult and pediatric outpatients):
  - Reduce duration of symptoms by 1 day
  - Decrease frequency of mild to moderate complications
    - Otitis media, bronchitis, antibiotic use
  - May decrease viral shedding
Oseltamivir
Treatment Effectiveness: Seasonal Influenza

- Effectiveness of oseltamivir treatment of hospitalized patients (retrospective, uncontrolled):
  - Reduction of hospitalization duration in elderly when Oseltamivir started <48 hours of onset (Hong Kong)
  - Reduction of mortality within 15 days after onset in elderly, including Oseltamivir treatment >48 hours after onset (Canada)
  - Oseltamivir treatment associated with survival in hospitalized patients (Thailand; confirmed by RT-PCR)
  - No controlled clinical trial data available

Lee at al., Antiviral Therapy 2007; McGeer et al., CID 2007; Hanshaoworakul et al., PLoS ONE 2009
Oseltamivir
Treatment Effectiveness: H5N1 Influenza

• Effectiveness of Oseltamivir treatment of severely ill hospitalized patients with lower respiratory tract disease (retrospective, uncontrolled):
  • Treatment associated with survival (Vietnam; WHO)
  • Earlier treatment associated with survival (Indonesia)
  • No controlled data available

➢ WHO recommends considering higher dosing, longer duration of treatment for severely ill H5N1 patients

Neuraminidase Inhibitor Chemoprophylaxis: Seasonal Influenza

- 70-80% efficacy in preventing illness after exposure (post-exposure chemoprophylaxis)
  - Oseltamivir and Zanamivir have similar efficacy in chemoprophylaxis
  - May not prevent asymptomatic virus infection - immune response may occur

- High effectiveness when chemoprophylaxis used to control outbreaks (e.g. nursing homes) with other measures
Antiviral Resistance

- Oseltamivir resistance can develop infrequently during treatment of seasonal influenza and H5N1
- Public health concern: are Oseltamivir-resistant influenza viruses transmitted in the community?
- Global circulation of Oseltamivir-resistant seasonal influenza A (H1N1) virus, since 2007 (not associated with treatment)
  - Oseltamivir resistance associated with mutation in neuraminidase gene (H274Y) [susceptible to Zanamivir]
  - 99% of seasonal H1N1 virus strains in the U.S. resistant to Oseltamivir (2008-2009)
    - Susceptible to Zanamivir, Amantadine, Rimantadine
Antiviral Resistance

- Pandemic H1N1 virus is resistant to Amantadine and Rimantadine
  - Oseltamivir resistance reported in one patient with pandemic H1N1 in Denmark (mild illness)
    - Patient was on Oseltamivir chemoprophylaxis
    - Resistance associated with H274Y mutation in neuraminidase gene [susceptible to Zanamivir]
  - Oseltamivir resistance in pandemic H1N1 virus reported in one case from Japan
  - No Oseltamivir resistance detected in pandemic H1N1 virus strains in the U.S.
# Summary of Antiviral Resistance, U.S. 2008-09

<table>
<thead>
<tr>
<th>Antiviral</th>
<th>Seasonal A (H1N1)</th>
<th>Seasonal A (H3N2)</th>
<th>Seasonal B</th>
<th>Pandemic H1N1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adamantanes</td>
<td>Susceptible</td>
<td>Resistant</td>
<td>No activity</td>
<td>Resistant</td>
</tr>
<tr>
<td>Oseltamivir</td>
<td>Resistant</td>
<td>Susceptible</td>
<td>Susceptible</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>Susceptible</td>
<td>Susceptible</td>
<td>Susceptible</td>
<td>Susceptible</td>
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</tbody>
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Antiviral Treatment Recommendations

- **Priority: Hospitalized Patients with suspected or confirmed pandemic H1N1 virus infection**
  - Treatment recommended with Oseltamivir or Zanamivir
  - Treat patients as soon as possible (duration: 5 days)

- **Outpatients with suspected or confirmed pandemic H1N1 virus infection who are at high risk for complications**
  - Persons with chronic pulmonary, cardiac, renal, hepatic, metabolic, hematological disorders; immunosuppression, pregnant women, children <5 years; adults ≥65 years
  - Treatment recommended with Oseltamivir or Zanamivir
  - Treat patients as soon as possible (duration: 5 days)
Antiviral Treatment Considerations

- Hospitalized patients with severe or progressive lower respiratory tract disease (ICU patients)
  - Oseltamivir or Zanamivir treatment
  - Consider higher dosing
    - Potential for high viral levels in lower respiratory tract
    - Potential for reduced GI absorption
    - No indication of safety concerns
  - Consider longer duration of treatment
    - Potential for prolonged viral shedding

*Treatment of pregnant women, infants <1 year old is recommended in the U.S.*
Antiviral Chemoprophylaxis

• Post-exposure chemoprophylaxis with Oseltamivir or Zanamivir can be considered:
  • Close contacts of cases who are at high risk for complications of influenza
  • Health care personnel, public health workers, first responders with unprotected close contact exposure to an ill person with pandemic H1N1 virus infection while in the infectious period
  • Chemoprophylaxis: 7-10 days after last known exposure
Antiviral Questions

• What is the clinical effectiveness of antiviral treatment?
  • Early (<48 hours of onset) versus late treatment?
  • In critically ill patients with complications?
    • Reduction in clinical course, reduction in mortality?

• What is the clinical benefit of higher antiviral dosing, longer duration of treatment?

➢ Clinical and virological data needed to inform antiviral treatment guidance
Summary

- Circulating pandemic H1N1 virus strains
  - Resistant to Amantadine, Rimantadine
  - Susceptible to Oseltamivir, Zanamivir

- Treatment of hospitalized patients and high-risk outpatients with pandemic H1N1 virus infection is recommended (limited data from seasonal and H5N1 influenza)

- Clinical and virological data are needed in patients treated with antivirals

- Post-exposure chemoprophylaxis can be considered for high-risk persons, health care personnel, first responders

- On-going monitoring for antiviral resistance is needed
Thanks for your attention!