Treatment and Prevention of Shingles

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The Goals of Antiviral Therapy

• Decrease severity and duration of pain caused by acute neuritis
• Promote more rapid healing of skin lesions
• Prevent new lesion formation
• Decrease viral shedding to reduce risk of transmission
## FDA-approved Antiviral Medications for Herpes Zoster

<table>
<thead>
<tr>
<th>Antiviral</th>
<th>Bioavailability</th>
<th>Dosing Frequency</th>
<th>Common Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir (Zovirax)</td>
<td>Poor</td>
<td>High (800 mg orally 5 times daily for 7-10 days)</td>
<td>Malaise</td>
</tr>
<tr>
<td>Valacyclovir (Valtrex)</td>
<td>Well absorbed, pro-drug of acyclovir</td>
<td>Low (1 g orally 3 times daily for 7 days)</td>
<td>Nausea, headache</td>
</tr>
<tr>
<td>Famciclovir (Famvir)</td>
<td>Well absorbed, pro-drug of penciclovir</td>
<td>Low (500 mg orally 3 times daily for 7 days)</td>
<td>Nausea, headache</td>
</tr>
</tbody>
</table>
Evidence for Efficacy of Antivirals Based on Controlled Trials

- Hasten resolution of lesions
- Reduce formation of new lesions
- Reduce viral shedding
- Decrease severity of acute pain
- No evidence for reduction of postherpetic neuralgia
Patients Most Likely to Benefit from Antiviral Therapy for Herpes Zoster

• Persons 50 years of age or older
• Patients with moderate to severe pain at onset of shingles
• Patients with severe rash with large numbers of lesions
• Patients whose face or eyes are involved or who have other complications
• Immunocompromised patients
# Antiviral Therapy for Herpes Zoster in Immunocompromised Patients

<table>
<thead>
<tr>
<th>Antiviral</th>
<th>Dose</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>10 mg/kg intravenously every 8 hours for 7-10 days</td>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>Foscarnet for acyclovir resistant VZV</td>
<td>40 mg/kg intravenously every 8 hours until lesions healed</td>
<td>Renal insufficiency, electrolyte abnormalities, nausea, vomiting, diarrhea, anemia, granulocytopenia, headache</td>
</tr>
</tbody>
</table>
Medications Used to Treat Acute Pain Associated with Herpes Zoster

<table>
<thead>
<tr>
<th>Medication</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-opioid analgesics</td>
<td>Acetaminophen, Naproxen, ibuprofen (NSAIDS)</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>Codeine, tramadol, oxycodone</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Gabapentin or pregabalin</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Nortryptiline, desipramine</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Prednisone</td>
</tr>
<tr>
<td>Topical therapy</td>
<td>Lidocaine patch (5%)</td>
</tr>
</tbody>
</table>
Use of Glucocorticoids with Antiviral Therapy for Herpes Zoster

• Some randomized-controlled trials have shown a reduction in acute pain, accelerated healing, improved performance of activities of daily living
• Studies have not shown a reduced incidence of postherpetic neuralgia
• Used for the treatment of CNS complications such as vasculopathy or Bell’s palsy
• Avoid in patients who can experience complications from steroids
# Treatment of Postherpetic Neuralgia

<table>
<thead>
<tr>
<th>Treatment Strategy</th>
<th>Medication</th>
<th>Caution or Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclic antidepressants</td>
<td>Nortryptiline, desipramine</td>
<td>Heart disease, epilepsy, glaucoma; the elderly</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Gabapentin, pregabalin</td>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>Opioids</td>
<td>Oxycodone</td>
<td>Potential for abuse and addiction</td>
</tr>
<tr>
<td>Topical</td>
<td>Lidocaine Capsaicin</td>
<td>Apply to intact skin Burning sensation</td>
</tr>
</tbody>
</table>
Vaccines for Varicella and Herpes Zoster

- Varicella vaccine, Varivax, approved by FDA in 1995 for prevention of chickenpox in persons ≥ 12 months
- Zoster vaccine, Zostavax, approved by FDA in 2006 to prevent shingles in persons ≥ 60
- Varicella vaccine developed in Japan as a live virus attenuated in cell culture (Oka vaccine)
- Zoster vaccine is the identical virus, but ~14-fold higher titer than varicella vaccine
- In 2008, CDC recommended routine vaccination among people aged ≥ 60
Shingles Prevention Study

- A randomized, double-blind, placebo-controlled clinical trial of 38,546 adults 60 years of age or older
- **Hypothesis**: the live attenuated Oka/Merck varicella-zoster virus vaccine would decrease the incidence and severity of herpes zoster and/or postherpetic neuralgia
Shingles Prevention Study Eligibility Criteria

Inclusion criteria:
• >60 year old (mean was 69 yr, range 59-99)
• History of varicella or lived ≥30 years in US

Exclusion criteria:
• History of zoster
• Immunocompromised
• <5 year life expectancy
Primary Endpoint of Zoster Vaccine Trial: Burden of Illness Score

BOI = a composite of the incidence, severity, and duration of pain caused by HZ

BOI = Area under the curve

Oxman et al JID 2008
Secondary Endpoint: Postherpetic Neuralgia

- Postherpetic neuralgia defined as pain or discomfort with a pain score $\geq 3/10$ persisting or appearing more than 90 days after onset of herpes zoster rash
Shingles Prevention Study Results

• Compared to placebo the zoster vaccine reduced
  1) the burden of illness by 61.1% (p<0.001)
  2) the incidence of postherpetic neuralgia by 66.5% (p<0.001)
  3) the incidence of herpes zoster by 51.3% (p<0.001)

• Vaccine was well tolerated, mild injection site reactions
Vaccine Reduces Burden of Illness Score, but Less Effective in Elderly

\begin{align*}
\text{Efficacy} & \quad \text{61.1\%} \\
& \quad (51.1\%-69.1\%) \\
& \quad \text{65.5\%} \\
& \quad (51.5\%-75.5\%) \\
& \quad \text{55.4\%} \\
& \quad (39.9\%-66.9\%)
\end{align*}

\begin{align*}
\text{Burden of Illness Score} & \quad 5.68 \\
& \quad 2.21 \\
& \quad 4.33 \\
& \quad 1.50 \\
& \quad 7.78 \\
& \quad 3.47
\end{align*}

\begin{align*}
\text{n} & \quad 19,247 \\
& \quad 19,254 \\
& \quad 10,356 \\
& \quad 10,370 \\
& \quad 8891 \\
& \quad 8884
\end{align*}

- Placebo
- Vaccine

\text{All subjects}
\text{Age 60–69}
\text{Age ≥70}

\text{Oxman et al JID 2008}
Vaccine Efficacy for Zoster Declines in Elderly

Vaccine Efficacy for Postherpetic Neuralgia Unchanged with Age

Oxman et al JID 2008
Pain in Persons with Zoster in Vaccine and Placebo Recipients

• Median duration of pain in persons who developed zoster was shorter in vaccine (21 days) than placebo group (24 days), p=0.03

• Degree of pain was less in vaccine recipients than placebo group (p=0.008)
Kaplan–Meier Estimates of the Effect of Zoster Vaccine on the Cumulative Incidence of Postherpetic Neuralgia (Panel A) and Herpes Zoster (Panel B) in the Modified Intention-to-Treat Population

Zoster Vaccine: Indications & Contraindications

Indications
• All persons ≥60 years old

Contraindications in persons with
• Hematologic malignancies- can be given if in remission and no chemotherapy or radiation for ≥3 months
• AIDS, or HIV and CD4<200 or <15%
• Cellular immunodeficiency (BMT, T cell deficiency)
• High dose immunosuppressive therapy (e.g. ≥20 mg of prednisone daily for ≥2 weeks), or anti-tumor necrosis factor therapy; wait 1 month after stopping therapy to vaccinate
• Allergy to vaccine components (neomycin or gelatin)
Zoster vaccine maintains its efficacy regardless of the age of the subject:

– The effect in “younger” subjects is mediated mostly by preventing zoster

– The effect in “older” subjects is mediated mostly by attenuating zoster, including PHN
Comparison of the Varicella-Zoster Virus-Specific Immune Responses to Herpes Zoster and to the Zoster Vaccine

Weinberg et al
JID 2009
Randomized-controlled Trial for Herpes Zoster Vaccine in Persons Aged 50-59 Years

- ZEST= Zostavax Efficacy and Safety Trial-evaluation of safety and efficacy of vaccine in 22,439 subjects aged 50 to 59 years
- Randomized to receive a single dose of vaccine or placebo
- Monitored for the occurrence of shingles for a median of 1.3 years post-vaccination
- Vaccine efficacy of 69.8%
- Approved by the FDA but not recommended by ACIP

Schmader KE Clin Infect Dis 2012
Long-term Persistence of Zoster Vaccine Efficacy

• Assessed vaccine efficacy in Shingles Prevention Study vaccine recipients (6,867) up to 11 years postvaccination
• Compared to SPS, for years 7 to 11 post vaccination, estimated vaccine efficacy decreased from
  – 61.1% (yr 4) to 37.3% (yr 11) for HZ burden of illness
  – 66.5% (yr 4) to 35.4% (yr 11) for incidence of postherpetic neuralgia
  – 51.3% (yr 4) to 21.1% (yr 11) for incidence of herpes zoster
• Statistically significant vaccine efficacy for BOI persisted into year 10, whereas efficacy for incidence of zoster persisted until year 8

Morrison VA et al CID 2015
Booster Dose of Shingles Vaccine Administered to Older Adults ≥ 10 Years After the First Dose

• Second dose of zoster vaccine administered to 200 participants ≥ 70 years old and compared to T cell immune responses in participants vaccinated for the first time
• For subjects ≥ 70 years old, VZV-specific T cell immunity (IFN-γ and IL-2 ELISPOTS) was significantly higher at baseline and after vaccination in the booster dose group
• The booster dose improved cellular immunity, but the effect on the incidence of zoster was not evaluated.

Levin MJ et al. JID 2016
Adjuvanted Herpes Zoster Subunit Vaccine in Older Adults ≥ 50

• Phase III, randomized, placebo controlled study of a vaccine containing VZV gp E and AS01\textsubscript{B} adjuvant system (HZ/su)
• Two IM doses of vaccine or placebo 2 months apart; mean follow-up 3.2 years
• Overall vaccine efficacy against herpes zoster 97.2%
• Vaccine efficacy in adults ≥ 70 years of age was similar to 50 to 59 and 60 to 69 age group

Lal H et al. NEJM 2015
Vaccine Efficacy against the First or Only Episode of Herpes Zoster Infection.

<table>
<thead>
<tr>
<th>Cohort and Age Group</th>
<th>HZ/su Group</th>
<th>Placebo Group</th>
<th>Vaccine Efficacy†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Participants</td>
<td>No. of Confirmed Cases</td>
<td>Cumulative Follow-up Period ‡</td>
</tr>
<tr>
<td><strong>Modified vaccinated cohort</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All participants in cohort</td>
<td>7344</td>
<td>6</td>
<td>23,297.0</td>
</tr>
<tr>
<td>50–59 yr</td>
<td>3492</td>
<td>3</td>
<td>11,161.3</td>
</tr>
<tr>
<td>60–69 yr</td>
<td>2141</td>
<td>2</td>
<td>7,007.9</td>
</tr>
<tr>
<td>70 yr or older</td>
<td>1711</td>
<td>1</td>
<td>5,127.9</td>
</tr>
<tr>
<td><strong>Total vaccinated cohort</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All participants in cohort</td>
<td>7698</td>
<td>9</td>
<td>25,584.5</td>
</tr>
<tr>
<td>50–59 yr</td>
<td>3645</td>
<td>3</td>
<td>12,244.9</td>
</tr>
<tr>
<td>60–69 yr</td>
<td>2244</td>
<td>5</td>
<td>7,674.1</td>
</tr>
<tr>
<td>70 yr or older</td>
<td>1809</td>
<td>1</td>
<td>5,665.5</td>
</tr>
</tbody>
</table>

* The total vaccinated cohort included all vaccinated participants for whom data related to efficacy end points were available. The modified vaccinated cohort excluded participants who did not receive the second dose of vaccine or who received a confirmed diagnosis of herpes zoster within 1 month after the second dose. Efficacy was calculated by means of the Poisson method.
† P<0.001 for all efficacy comparisons with placebo. Vaccine efficacy in each age group was adjusted for region. Overall vaccine efficacy was adjusted for age group and region.
‡ Data were censored at the time of the first confirmed diagnosis of herpes zoster.

Summary: Treatment and Prevention of Herpes Zoster

- Antiviral agents reduce the duration of lesions and severity of disease, but not the incidence of postherpetic neuralgia
- Improved treatments are needed for postherpetic neuralgia
- Herpes zoster vaccine is effective, but uptake has been suboptimal
- New subunit vaccine may have improved efficacy compared with current live attenuated vaccine and may be used in immunocompromised persons
- The efficacy and timing of booster doses of the zoster vaccine needs to be determined
Zoster Vaccine: Unanswered Questions

• Is the vaccine appropriate in persons ≥80 years old?
  Efficacy for zoster 18%, for PHN 39%
• How long will the vaccine be effective (booster doses)?
  A follow-up study showed that the reduction in risk for HZ remained significant at least for 8 years after vaccination
• Can the vaccine be used safely in immunocompromised persons?
  Studies ongoing; preferable to give it 2-4 weeks before starting immunosuppressive therapy
• Will zoster be significantly reduced when varicella vaccine replaces wild-type varicella?
  Vaccine strain of zoster reactivates less frequently than wild-type