Herpes Zoster: The disease and the vaccines

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Declarations

• Chair, Publications committee, GSK Shingrix ZoE50 and ZoE70 trials
• Member, Global Adult Vaccine Advisory Board, Merck
• Chair, Zostavax Advisory Board, BioCSL/Sequirus

Take home message

• From November 2016
• Management of herpes zoster demands immunization of all people between 70 and 79 with Zostavax
• To prevent: Herpes zoster
  • Post-herpetic neuralgia
• Contraindications: Severely immune-compromised patients
• Vaccine efficacy 50-65% so breakthroughs may occur and require antiviral treatment, less severe though
• Duration ~ 10 years so a booster may be necessary
• A new competing vaccine with different characteristics may be available in 2018

Zoster: Latency and Reactivation

Herpes Zoster (shingles)

• Usually unilateral, vesicular cutaneous eruption with a dermatomal distribution
• Acute pain accompanies the rash in >90% of individuals aged over 50 years
• The most common complication is post herpetic neuralgia (PHN), defined as pain persisting for 90 or more days after rash onset
• >50% of population >85 years will get zoster

Risk factors for Herpes Zoster

• Increasing age
  • Less opportunity for boosting?
    • Less frequent exposure to varicella cases
    • Less frequent contact with multiple ill children
• Decline in cell-mediated immunity
  • Immunosenescence
  • Cell-mediated immunosuppressive disorders
  • Haematological malignancies
  • Immunosuppressive drugs
  • HSV: 12-17 fold increased risk

References:

Gnann, Jr. & Whitley
Dworkin et al.
Thomas & Hall
Herpes zoster and PHN increase with age in Australia

Stein A et al. Vaccine 2009

Rate of HZ Complications

<table>
<thead>
<tr>
<th></th>
<th>Incidence Rate*</th>
<th>Incidence Rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic (incl PHN)</td>
<td>298</td>
<td>10.7</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>41</td>
<td>2.0</td>
</tr>
<tr>
<td>Ocular Involvement</td>
<td>14</td>
<td>0.7</td>
</tr>
<tr>
<td>Sacral Dermatome Involvement</td>
<td>6</td>
<td>0.4</td>
</tr>
<tr>
<td>Visceral Complications</td>
<td>9</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Birch C et al, Sex Transm Infect 2003;79:298-300

Zoster Diagnosis

- Clinical diagnosis alone
  - ‘shingles’
- Laboratory diagnosis needed in
  - immunosuppressed patients
  - less common & atypical presentations
  - (eg. genital*, HZ oticus)
  - complicated presentations (eg. dissemination, CNS disease)
  - Vesicle NAT or IF

Birch C et al, Sex Transm Infect 2003;79:298-300

Five ‘ages’ of vaccines

- Infancy: multiple
- Adolescence: papillomavirus, HSV, EBV
- Pregnancy
- Older adults: influenza, pneumococcus, shingles
- Any, Epidemic: influenza, Ebola, Dengue, ?Zika

Types of vaccines

- Whole virus
- Live attenuated
- Inactivated
- Split
- Sub-unit

Adult immunization is not prioritized

<table>
<thead>
<tr>
<th>US Pediatric Coverage Rates %</th>
<th>US Adult Coverage Rates %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polio (3 doses)</td>
<td>93</td>
</tr>
<tr>
<td>Hep B (3 doses)</td>
<td>90</td>
</tr>
<tr>
<td>Varicella (1 dose)</td>
<td>90</td>
</tr>
<tr>
<td>DTaP (4 doses)</td>
<td>94</td>
</tr>
<tr>
<td>DTaP (4 doses)</td>
<td>83</td>
</tr>
<tr>
<td>PCV (1 dose)</td>
<td>92</td>
</tr>
<tr>
<td>PCV (1 dose)</td>
<td>92</td>
</tr>
<tr>
<td>Adult pneumonia (5+ yrs, 1 dose)</td>
<td>35</td>
</tr>
<tr>
<td>Tetanus/Boost (5+ yrs, 2 doses)</td>
<td>10</td>
</tr>
<tr>
<td>Adult pneumonia (5+ yrs, 1 dose)</td>
<td>98</td>
</tr>
<tr>
<td>Full adult schedule*</td>
<td>68</td>
</tr>
</tbody>
</table>

CDC. MMWR. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6433a1.htm
CDC. MMWR. https://www.cdc.gov/mmwr/volumes/65/ss/ss6501a1.htm

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2. CDC. MMWR. http://www.cdc.gov/mmwr/volumes/65/ss/ss6501a1.htm
Shingles Prevention Study (SPS)

- A double-blind, placebo-controlled trial
  - 22 Sites
- Live, attenuated VZV vaccine
  - Oka/Merck strain (Median = 24,600 pfu)
  - 14-fold greater titer than childhood vaccine
- Subjects = 38,500
  - Median age = 69 years
  - 60-69 years = 20,750
  - ≥ 70 years = 17,800 (46%)
  - ≥ 80 years = ~2500 (>6.5%)

Oxman et al. NEJM 352; 2271: 2005

SPS: Endpoints

- Herpes Zoster (incidence/1000/year)
  - Mean follow-up = 3.13 years
- Burden of Illness (BOI)
  - Sum of all severity of illness scores for each of two treatment groups - vaccinees and placebo recipients
- Post-herpetic neuralgia (PHN)
  - Significant pain (≥ 3 on ZBPI)
  - ≥90 days after rash onset
  - 95% of subjects completed the study

SPS: Conclusions

- In the full SPS population Zostavax significantly altered the natural history of zoster
  - Prevented zoster in the younger group of vaccinees (60-69)
  - Prevented OR attenuated zoster in the older group of vaccinees (>70)
  - Efficacy and safety essentially replicated in several large postmarketing studies (Kaiser Permanente, CA etc)
  - Low rates of severe injection site reactions (~1%)

SPS ZEST Study in 50-59 year olds:
HZ incidence decreased by 70%, HZ pain by 73% (ie greater VE)

Duration of effectiveness of herpes zoster vaccine
Zoster vaccines for Immunocompromised patients

- Zostavax, ACIP Recommendations:
  - Live attenuated vaccines, such as Zostavax, contraindicated for severely immunocompromised
  - >20mg prednisone daily for >2 weeks,
  - Hemopoietic Stem Cell Tx
  - Hematologic malignancies not in remission for >3 months, esp advanced Hodgkins disease, (ie cytotoxic therapy within past 3 months), including CLL
  - T cell immunodeficiency, including HIV pts with CD4<15%

- Cf HZ/su GSK (Recombinant VZV gE + adjuvant AS01B) – not contraindicated and safe in immunocompromised (HSCT, HIV <15% CD4)

Zostavax: issues

- Moderate efficacy, lower in >80
- Duration of effectiveness ?8-10 years
  - Need a booster, probably at 10 years
- Unsafe in severely immunocompromised
- Safety in moderately immunocompromised pts needs better definition

Zostavax in Australia

- Nov 2016: Approved for National Immunization program
- 70-79 yo with catchup (private 50 years)
- Now >50% vaccine dose distribution within a year
- Implications for new vaccine

Recombinant VZV glycoprotein E + T cell adjuvant

Phase I/II: T cell responses to HZ/su (gE/AS01) but not gE alone diminish little with advancing age

T cell stimulating adjuvant Systems

- Combinations of:
  - Classical adjuvants: aluminum salts, emulsion, liposomes.
  - Immunostimulants: MPL, QS21, (CpG).

(d)MPL

QS21
Phase III Trials of GSK HZ/su (Shingrix)

- Placebo - RCT in Europe, USA, Asia, Australia
- Two doses IMI two months apart, 96% compliance
- ZoE-50: 15,411 evaluable adults > 50 years, stratified in 10 year blocks,
- ZoE-70: 13,900 adults >70 years focusing on PHN
  - two papers published in NEJM,
  - abstract on immunology presented to IHW

ZOE-50: GSK Herpes Zoster (HZ/su) Vaccine Efficacy

ZOE-70 trial: efficacy against HZ and PHN

13,900 Adults >70, average age 75.2 years
- vaccine efficacy = 90% (95% CI 84-94)
  - similar in 70-79 and >80
  - efficacy against PHN: 89% (69-97)
  - ie no additional efficacy against PHN cf HZ
- Efficacy against PHN in (Pooled) Adults>50 : 91% (76-98)
  - No cases <70 years
  [Cunningham, Lal, Levin ..Heineman et al NEJM 2016]

ZOE-70: Risk of development of Herpes zoster after vaccination


ZOE-70: Risk of development of post-herpetic neuralgia after vaccination

HZ/su in immunocompromised patients

- Phase I-II trials of HZ/su in autologous HSCT for HD, AML, Myeloma:
  - comparable immunogenicity (antibody and CD4 T cells) and reactogenicity to immunocompetents; maintained for 1 year
- Phase III trial data soon to be submitted
- HIV: HZ markedly diminished by ART: still 3-5x risk if CD4<200
  - Phase I-II trials HZ/su in 3 cohorts: good immunogenicity maintained for duration, 18 mo. No worsening of CD4 counts, safe
- Need to compare Zostavax vs HZ/su in mildly immunocompromised patients respectively (ie autoimmune diseases and Rx with biologics)

Shingrix, HZ/su: issues

Two doses: likely compliance in real world setting,
Efficacy after a single dose?
Will high reactogenicity (severe local: 9%) reduce uptake?
Duration of efficacy to be determined (T cell immunogenicity plateaux for 3-9 years- promising)
- long term followup trials commenced
Can it be used as a booster after Zostavax?
Risk of auto-immunity with new adjuvants: needs long term post marketing surveillance
Efficacy in severely immunocompromised: phase III trial results available soon

HZ/su: Implications

- HZ/su development and trialling confirms several scientific hypotheses:
  - vaccines consisting of a single pathogen protein and adjuvant(s) can be efficacious- and more than a live attenuated vaccine
  - such a combination may cut through immunosenescence = hope for other vaccines in older subjects
  - Pathogen/vaccine/adjuvant immunology is of increasing relevance for (rational) vaccine development

Take home Message

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- Duration ~ 10 years so a booster may be necessary
- A new competing vaccine with different characteristics may be available in 2018
HZ/su: Remaining Immunologic questions

- Duration of humoral and CD4 T cell responses (>9 years)?
- Mechanisms:
  - Relative importance of T cells in boosting antibodies vs other mechanisms
  - Role and importance of polyfunctional CD4 T cells
  - Is there a CD8 T cell response?
  - Role of innate immune responses (NK, mono, DCs)

- Immune correlates of protection difficult to define because few breakthrough HZ cases
- However difference in protection against HZ in Zostavax and HZ/su correlates with CD4 T cell response: (2x vs. 39x baseline)
- ? with CD8 T cell responses: available soon
- Will these responses be improved after HZ/su boosting of Zostavax?

Antiviral treatment of herpes zoster

- Oral famciclovir, valaciclovir or, if complications, IV aciclovir
- Treat up to 72 hpi or if new vesicles appearing, disseminated lesions, HZ ophthalmicus/oticus
- Check renal function and modify dosage if necessary
- Treat pain with systemic analgesics, no topical LA, capsaicin
- If pain moderate/severe: add amitryptaline, pregabalin
- If pain prolonged > 4 weeks refer to pain specialist
- If ophthalmic zoster, refer to ophthalmologist
- Consider immunosuppression, pregnancy
- No evidence antivirals prevent PHN defined as pain >90 days

Laboratory diagnosis

- Antigen detection (IF etc)
- Nucleic acid testing (NAT)
  - VZV
  - Multiplex (eg HSV 1/2, VZV etc)
- Serology
  - VZV-specific IgM
  - ‘immune status’ (FAMA, gpELISA)
  - (avidity)
  - 95% of young Australian adults (~25 YO) immune

Complications of Zoster

- Neurologic
  - PHN
  - Limb weakness
  - Peripheral palsies
  - Sensory loss
  - Meningitis
  - Myelitis
  - Encephalitis
  - Hearing loss

- Ophthalmic
  - Visual impairment
  - Ptosis
  - Cutaneous
  - Scarring
  - Bacterial superinfection
- Disseminated disease
  - Pneumonia
  - Hepatitis

The Pivotal Phase 3 Program: ZOE-50 and ZOE-70

Study Design and Objectives

ZOE-50

- Randomized, observer-blind, placebo-controlled, multicenter, multinational (North America, Europe, Latin America, Asia, Australia)
- Primary objectives:
  - HZ efficacy in persons ≥50 YOA
  - PHN efficacy in 70+
  - HZ efficacy in 70+

ZOE-70

- Randomized, observer-blind, placebo-controlled, multicenter, multinational (North America, Europe, Latin America, Asia, Australia)
- Primary objectives:
  - HZ efficacy in persons ≥70 YOA
  - PHN efficacy in persons ≥70 YOA

- Actual enrollment:
  - ZOE-50: 16,160 enrolled
  - ZOE-70: 14,816 enrolled

Subjects ≥70 years of age were randomly assigned to ZOE-50 or ZOE-70.

HZ, herpes zoster; PHN, postherpetic neuralgia; YOA, years of age.

Laboratory diagnosis

- Antigen detection (IF etc)
- Nucleic acid testing (NAT)
  - VZV
  - Multiplex (eg HSV 1/2, VZV etc)
- Serology
  - VZV-specific IgM
  - ‘immune status’ (FAMA, gpELISA)
  - (avidity)
  - 95% of young Australian adults (~25 YO) immune
VZV Pathogenesis

- Entry through upper respiratory tract
- 10-21 day incubation
- Travels to regional lymph nodes, then to spine via posterior primary sensory nerve
- Secondary viremia (MN cells)
  - to dermal microvascular vesicular rash
  - Replication in epidermal cells, entry into nerve endings & transport to DRG to establish latency in sensory neurons

Trials in Progress

- Co-administration with other ‘adult’ vaccines
  - Tdap, influenza, pneumococcal conjugate vaccine
- Immunization of previous Zostavax recipients
- Safety and immunogenicity in other severe immunocompromising conditions
  - renal transplant
  - solid organ tumours
  - Hematologic malignancies

Duration of protection of Zostavax

- Short term Persistence Sub study:
  - 7310 Zostavax / 6950 placebo recipients, 89% of which accepted the offer of Zostavax; all participants followed for 4-7 years
  - VE = 39.6% for zoster, 60% for pHN and 50% for BOI
- Long term Persistence Sub study:
  - Open label Multicentre study, followed up 6867 vaccine recipients for 7-12 years.
    - No unvaccinated concurrent control group so original SPS placebo recipients used as controls.
    - VE = 21% for zoster, 35% for PHN and 37% for BOI
    - ie provides evidence for waning of efficacy but probably significant to 8 years when analysed annually
- Booster dose at 10 years: in >70 year old CMI responses were stimulated to levels similar to those of a first response in 60-69 YO

Age dependent incidence of herpes zoster and PHN in Australia

- Progressive decline in systemic immunity
- Increased prevalence of cancer, autoimmune and chronic diseases
- Poor response to immunization
- Increased vulnerability to common infectious diseases (influenza etc)
- Mechanism:
  - decline in innate immunity: NK cells, DCs, PMNs
  - naive T cells less diverse, more memory T cells, signalling defects
- Role of late reactivation of CMV still controversial
- Role of adjuvants (cf MF59 for influenza)
Incidence of Herpes zoster is increasing globally. Trend in zoster ED visits - NSW

- Rates of ED visits increased with age.
- Most ED visits are not admitted.
- Increasing trend in non-admitted ED visits over time, most prominent in older population.

Nature of Pain in PHN

<table>
<thead>
<tr>
<th>Patients using descriptor (%)</th>
<th>(n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous</td>
<td>49%</td>
</tr>
<tr>
<td>Burning</td>
<td>40%</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>18%</td>
</tr>
<tr>
<td>Stabbing</td>
<td>18%</td>
</tr>
<tr>
<td>Shooting</td>
<td>13%</td>
</tr>
<tr>
<td>Sharp</td>
<td>6%</td>
</tr>
</tbody>
</table>

Clinical Manifestation of Zoster

- Prodromal Phase: Acute pain
- Resolves
- Acute Phase: Characteristic dermatomal rash
- Complications: May or may not occur; most common is PHN

Nature of Pain in PHN

- Continuous
- Burning
- Throbbing
- Paroxysmal
- Stabbing
- Shooting
- Sharp

Efficacy in all age groups ≥50 years old (ZOE-50)¹⁻³

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Shingrix group</th>
<th>Placebo group</th>
<th>Vaccine efficacy (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50</td>
<td>6 (7344)</td>
<td>208 (7415)</td>
<td>97.2% (93.7-99.0)</td>
</tr>
<tr>
<td>≥60</td>
<td>3 (3852)</td>
<td>123 (3890)</td>
<td>97.6% (92.7-99.6)</td>
</tr>
<tr>
<td>≥70</td>
<td>1 (1711)</td>
<td>48 (1724)</td>
<td>97.9% (87.9-100.0)</td>
</tr>
</tbody>
</table>

Efficacy in all age groups ≥70 years old

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>Shingrix group</th>
<th>Placebo group</th>
<th>Vaccine efficacy (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>70-79*</td>
<td>19 (5483)</td>
<td>216 (5054)</td>
<td>95.3% (86.0-94.9)</td>
</tr>
<tr>
<td>≥80</td>
<td>6 (1782)</td>
<td>68 (1792)</td>
<td>95.8% (90.2-97.2)</td>
</tr>
</tbody>
</table>

¹ Pre-specified, Pooled Analyses from ZOE-50 and ZOE-70

References

7. Study #19-2207.
Pathogenesis of Herpes zoster

- **VZV**
  - latent within neurones mainly (2-5 copies/cell) reactivation
  - Usually only once (5% → second)
  - Different to HSV but mechanism unknown
  - Necrosis and inflammation in nerve root, DRG and nerve

- **VZV** → No apoptosis of infected neurones in vitro
  - Neurone/support cell lysis in DRG is probably immunopathologic

SPS: Efficacy

- **HZ Incidence**
  - 51.3% (44.2 – 57.6%)

- **Burden Of Illness**
  - 61.1% (51.1 – 69.1%)

- **Post Herpetic Neuralgia**
  - 66.5% (47.5 – 79%)

Licensure, availability and uptake worldwide

- USA: ACIP recommendation: immunize all immunocompetent persons≥60 with one dose of Zostavax
  - over 25 million doses distributed since 2006
  - overall uptake: 10.0% in 2009, 14.4% in 2010, 2014-24%

- UK: Sept 2013: Funded immunization program: all people > 70 and catchup cohort >79

- Australia: National Immunization Program funded for all i/c people >70 from Nov 2016; Catchup 71-79; Private market >50 since 2008

Minimal decline in efficacy up to 4 years post initial vaccination

Vaccine efficacy by year post vaccination

<table>
<thead>
<tr>
<th>Year</th>
<th>Shingrix VACCINE GROUP</th>
<th>Placebo GROUP</th>
<th>Vaccine efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>95.7% (90.9 – 99.8)</td>
<td>99.8% (90.9 – 99.8)</td>
<td>73.6% (68.0 – 78.4)</td>
</tr>
<tr>
<td>Year 2</td>
<td>92.0% (82.8 – 96.9)</td>
<td>96.9% (82.8 – 96.9)</td>
<td>84.7% (73.3 – 92.9)</td>
</tr>
<tr>
<td>Year 3</td>
<td>92.0% (82.8 – 96.9)</td>
<td>96.9% (82.8 – 96.9)</td>
<td>87.6% (75.4 – 95.4)</td>
</tr>
</tbody>
</table>

HZ/su as a booster following Zostavax?

- Important where high ZV coverage: data soon to be published
- **HZ/su after natural herpes zoster (physician documented):**
  - no safety concerns but high reactogenicity as for ZOE 50/70
  - good response rate antibody to vaccine for patients >50: 90.2%
  - similar across all age groups
One month post-dose 2, 93.3% of HZ/su recipients ≥50 YOA met the criteria for vaccine response.

\[ \text{VRR, vaccine response rate} \geq 2\text{-fold increase in gE-specific CD4}^+ \text{frequencies as compared to pre-vaccination levels; or} \]
\[ \geq 2\text{-fold above the cut-off (320/10} \text{gE-specific CD4}^+) \]

Sustained CD4 T cell Response at 9 years

- Both cellular and humoral immune responses persisted through 9 years
- Immune responses were stable since year 4
- Immune response persistence above baseline was independent of age (60-69 and ≥70 YOA)