

Herpes Zoster and the Zoster Eye Disease Study (ZEDS)

Elisabeth J Cohen MD Professor, Vice Chair for Faculty and Academic Affairs Department of Ophthalmology, NYU Grossman School of Medicine NYU Langone Health, New York, NY



Educational Objectives

- 1. To describe complications of herpes zoster.
- 2. To discuss study of suppressive valacyclovir to reduce complications of herpes zoster ophthalmicus
- 3. To discuss current recommendations for vaccination against zoster and challenge of underusage



I have no financial disclosures

Funded by NEI/NIH, National Shingles Foundation



Herpes Zoster (HZ) / Shingles

Common disease

- <u>>1,000,000</u> new cases/year in the United States
 - 8 percent Herpes Zoster Ophthalmicus (HZO)
- >95 percent of adults age 40+ in U.S. have had varicella and are at risk for HZ
- 1 in 3 in U.S. will have zoster
 - -1 in 2 age 85+

More common (~2x), severe in immunocompromised persons

> 90 percent of people with HZ are <u>not</u> immunocompromised

Misconception #1

- Healthy people are not at risk for zoster and its potentially disabling sequelae—we are!
- School of Medicine



Incidence HZO and HZ 1994–2018

Kong CL. Ophthalmology 2020;127:324. Thompson RR. Clin Infect Dis 2020 Aug 23. Harpaz JID 2018:218 (Suppl 2) S57

HZO

- Increased age 31-60 years old since 2007
- Men 0.74 rate women
- Blacks, Hispanics 0.75, 0.64 compared to whites

ΗZ

- No acceleration of increase after varicella vaccine
- Median age 56, 60 percent women
 25 percent age 43–56 years old
- Decrease <21, >60 since 2007

Need to vaccinate starting age 50!





Figure 1. Incidence rate of herpes zoster by age, 1994 to 2018

Age at Onset of Zoster

<u>Rate</u> goes up with age, but <u>number</u> of cases highest in 50s

- Yawn Neurology 2013; 81:928 (Figure 1)
- Insinga J Gen Intern Med 2005;20:748-53
- Ghaznawi Ophthalmology 2011;118:2242

Misconception #2

-HZ is only a disease of the elderly—it affects a large number of people in their prime too!







Complications of HZ: Postherpetic Neuralgia (PHN)

- Defined as pain/itch beyond 3 months after onset of zoster
- Most common complication of zoster
 - -Occurs in ~30 percent of HZO, mostly age 65+
 - Borkar Ophthalmology 2103; 120:451-6
- Systematic reviews of risk factors for PHN
 - -Age, severity of prodomal and acute pain, rash, HZO
 - Forbes Pain. 2016; 157:30-54, Kawai Int J Infect Dis. 2015; 34: 126-31
- Zoster risk factor for development of major depression
 - -Chen, M. H. Psychosom Med, 2014; 76:285-91
- Zoster is most common cause of suicide due to pain in people age 70 years and older

-Hess, TM. Minn Med. 1990; 73:37-40



Anecdote

"My mother worked full time to age 67.... She then got very ill with shingles.... She was in severe pain.... You could not even touch her hair or face.... She was never the same.... The chronic pain caused her to sleep for most of the day.... The pain never really went totally away.... I received the vaccine about 2 years ago, and pray I never get the disease. Neither polio, meningitis, or rheumatoid arthritis stopped my very active mother, but the shingles destroyed her life."

KC 2017



Zoster Risk for Stroke, Cardiovascular Disease

Nagel JID 2018: 218 (Suppl2) S107; Warren-Gash S102

Zoster long-known risk factor for stroke

- 55 percent-2x including stroke within 1–3 months, decreasing over 6–12 months
 - Yawn Mayo Clin Proc 2016; 91:33
- 8x risk stroke 1 month age 18-49 years
 - Patterson Mayo Clin Proc 2019; 94:763
- Should HZ patients have prophylactic antiviral treatment for 1 year, especially if <50 years old??
 - Nagel Mayo Clin Proc 2019; 94:742-44
- 2–4x risk stroke after HZO vs. HZ

Giant cell arteritis may be VZV vasculopathy of temporal artery

• Gilden, White, Khmeleva. Neurology. 2015; 84:1948

Zoster risk for cardiovascular disease

- Breuer. Neurology 2014;82:1.
- Wu P-H. J Clin Med 2019; 22:547 (short-term)
- Curran SG J Am Heart Ass. 2022; 11: e027451 (long-term)

NYU Grossman School of Medicine



Zoster as Risk Factor for Dementia

The association of Herpes Simplex Virus (HSV) and VZV infection with dementia: a nationwide retrospective cohort study

- Korea 2006–2017
- Hazard Ratio (HR): HSV 1.38, VZV 1.41 (95 percent CI: 1.37-1.46), especially eye, CNS, complicated VZV, including risk of Alzheimers and vascular dementia – Shin E Alzheimers Res Ther. 2024; 16:57

HZ virus infection and risk of developing dementia: a systematic review and metaanalysis

- Prevalence of dementia in HZ vs. HZ-free group
- No significant difference overall
- HZO had increased incidence of dementia
 - RR (relative risk): 6.25, 95 percent CI: 1.30-30.19, p = 0.02
 - Elhalag RH Medicine. 2023; 102:e34503



Possible New Treatment for HZO

- The Zoster Eye Disease Study (ZEDS), funded by NEI in 2016, to conduct a multicenter, randomized, placebo-controlled clinical trial (RCT) to determine whether prolonged, suppressive valacyclovir treatment reduces complications of HZO, including eye disease and/or postherpetic neuralgia
- Purpose to determine high-quality, evidence-based, new standard of care regarding suppressive antiviral treatment for HZO



ZEDS Study Structure

- 95 Participating Clinical Centers (PCCs) in U.S., Canada, and New Zealand
- Coordinating Center (CC) at NYU Langone Health
- Study Chair: Elisabeth Cohen, Co-Chair Bennie Jeng, U Penn
 - -Multiple PIs: Judith Hochman, Andrea Troxel, CC NYUSoM, NYULH
 - Executive Committee: James Chodosh, Kathryn Colby, Anat Galor, Todd Margolis, Alice Matoba, Stephen McLeod, Shahzad Mian, David Warner
 - -Medical monitor: Michael Perskin
 - -Clinical Event Review Committee: Debbie Jacobs, Chair
 - -DSMC of NEI, FDA IND



Background and Rationale of ZEDS

- Acute high-dose oral antiviral treatment is recommended for HZO, but there is no standard approach to antiviral treatment for ocular complications of HZO.
- Rationale of the ZEDS
 - First: Relatively recent knowledge of infectious pathogenesis of complications of HZ and HZO
 - Second: Significant benefit of suppressive antiviral treatment in reducing recurrent herpes simplex virus (HSV) eye disease in HEDS
 - New Eng J Med 1998; 339:300-6
 - HZO and HSV keratitis, caused by different herpes viruses, are analogous in many ways.



ZEDS Overview

- Double-masked, multi-center, randomized controlled trial (RCT)
- Immunocompetent adults ≥ 18 years of age
- History of typical unilateral rash
- Episode in medical record within the year prior to enrollment of keratitis or iritis
- Randomized 1:1 ratio to suppressive valacyclovir 1000 mg daily or placebo for one year of treatment and 18 months of follow-up, with study visits every 3 months
 - Randomized in 4 strata within center
 - Age of <u>onset</u> of HZO: < 60 years vs. \geq 60 years
 - Time since onset at <u>enrollment</u>: < 6 months vs. \ge 6 months
 - Rationale for strata included in statistical analysis plan
 - Expected ~50 percent < 60, disease manifestations vary by age
 - Expected greater benefit in recent-onset disease





Primary Objective and Endpoint

To evaluate whether or not 12 months of suppressive valacyclovir treatment, compared with placebo, delays time to first occurrence by 12 months of new or worsening of specific disease manifestations of HZO.

- Dendriform epithelial keratitis (DEK)
- Stromal keratitis (SK)
- Endothelial keratitis (EK) (disciform keratitis)
- Iritis (IR)
- Stromal keratitis with ulceration (SKU)
 - SK, EK, and IR required substantial increases in treatment
 - Primary endpoints reviewed and adjudicated by masked Clinical Event Review Committee

Secondary objective: To evaluate whether there is persistent treatment benefit at 18 months and 6 months after cessation of treatment





Corneal Disease Endpoints







Second Aim: Postherpetic Neuralgia

To test the hypothesis that suppressive treatment for 12 months with oral valacyclovir 1000 mg daily reduces the incidence, severity, and duration of PHN compared to placebo at 12 and 18 months (secondary objectives) in patients with HZO





Top Enrolling PCCs by Number Enrolled

| PCC # | PCC Name | PI | Green Light Letter Sent | Number Enrolled |
|-------|--|---------------------------|-------------------------|-----------------|
| 039 | University of Michigan | Shahzad Mian, MD | 1/8/2018 | 19 |
| 088 | Clinique Axe Visuel | Mazen Choulakian | 8/29/2019 | 17 |
| 117 | UAMS Jones Eye Institute | Dave Warner, MD | 3/10/2020 | 16 |
| 007 | Mayo Clinic - Rochester | Keith Baratz, MD | 10/18/2017 | 16 |
| 014 | Cornea Consultants of Nashville | Mark Ewald, MD | 9/7/2017 | 16 |
| 060 | Dartmouth Hitchcock Medical Center | Donald Miller, MD | 12/28/2017 | 15 |
| 130 | University of Auckland | Jay Meyer, MD | 9/21/2020 | 14 |
| 079 | Virginia Eye Institute | Christopher Estopinal, MD | 8/21/2018 | 14 |
| 051 | Pacific Eye Surgeons | Mark Sherman, MD | 9/12/2017 | 13 |
| 053 | Johns Hopkins Wilmer Eye Institute | Divya Srikumaran, MD | 5/8/2018 | 12 |
| 063 | Finger Lakes Ophthalmology | Holly Hindman, MD | 11/21/2017 | 12 |
| 038 | Baylor College of Medicine | Alice Matoba, MD | 9/27/2017 | 12 |
| 067 | Verdier Eye Center | Ann Renucci, MD | 9/7/2017 | 12 |
| 044 | NYU Langone Medical Center | Christina Prescott, MD | 9/6/2017 | 12 |
| 090 | CHUM | Marie-Claude Robert, MD | 1/14/2020 | 11 |
| 072 | Loma Linda University Eye Institute | Frank Hwang, MD | 4/24/2018 | 11 |
| 086 | UBC/Vancouver General Hospital | Alfonso lovenio, MD | 1/9/2020 | 11 |
| 010 | OHSU - Casey Eye Institute | Afshan Nanji, MD | 12/28/2017 | 10 |
| 042 | Medstar Georgetown University Hospital | Aruoriwo Oboh-Weilke, MD | 10/12/2017 | 10 |
| 066 | UT Southwestern | Jeremy Bartley, MD | 9/29/2017 | 10 |
| 045 | Ophthalmic Partners | Irving Raber, MD | 9/7/2017 | 10 |





Data Summary: Accrual by Strata

| Strata | Number of Randomized Participants | Percent of Participants | |
|----------------|--------------------------------------|-------------------------|--|
| All Strata | 527 | 100 | |
| < 60y, Recent | 162 | 31 | |
| < 60y, Chronic | 124 | 24 | |
| ≥ 60y, Recent | 138 | 26 | |
| ≥ 60y, Chronic | 103 | 20 | |





Baseline Characteristics at Enrollment

Prescott, Cohen, Hochman et al., Cornea 2024 Feb 27 online (2024; 00:1-8)

- 50 percent of randomized participants are female
- Both genders represented in each of the 4 strata
- 87 percent of participants are White
- 26 participants (5 percent) are Hispanic or Latino
- Median age at randomization: 60 (Q1–Q3: 50–68)
- 91 percent had received acute recommended antiviral treatment
- 79 percent of participants did not receive zoster vaccine prior to enrollment
- 8 percent of participants reported varicella vaccine prior to enrollment





Confirmed Endpoints

Dendriform Epithelial Keratitis (DEK), Stromal Keratitis (SK), Endothelial Keratitis (EK), or Iritis (IR)







Results



Flow of Participants Through Study

| Screened for eligibility | 651 |
|--|-----|
| Excluded | 124 |
| • Randomized 52 | 7 |
| – Valacyclovir | 266 |
| – Placebo | 261 |

• All received assigned study med and included in intention to treat analysis

Follow-up

| Withdrawn from study | | |
|--|----|--|
| – Valacyclovir | 29 | |
| – Placebo | 38 | |
| Stopped study med | 79 | |
| – Valacyclovir | 35 | |
| – Placebo | 44 | |
| | | |

- No study medication-related serious adverse events
- Completed study (527-67) 460





Primary Endpoint Analysis: Kaplan Meier by Treatment Overall

- No significant treatment benefit in reducing new/worsening SK, IR, DEK, and EK at *primary endpoint* of 12 months of treatment by log-rank test after adjusting for strata (p = 0.09), but significant benefit for secondary endpoint at 18 months (p = 0.03)
- **12 months: HR: 0.77**, 95 percent CI: 0.56-1.05, p = 0.09
- 18 months: HR: 0.73, 95 percent CI: 0.55-0.97, p = 0.03



Treatment - Placbo - Valacyclovir





Primary Endpoint Analysis: Kaplan Meier Curves by Treatment Within Strata





Subgroup Analyses at 12 (above) and 18 months (below)

| Subgroup | Placebo (N = 261) | Valacyclovir (N = 26 | 6) | HR (adjusted 95% CI) | | |
|--|---|---|-----------------------------|---|--|--|
| Sex | | | 1 | | | |
| Male | 34% | 33% | | 0.93 (0.61 to 1.41) | | |
| Female | 32% | 23% | _ | 0.66 (0.41 to 1.05) | | |
| Strata | | | | | | |
| <60y, Chronic | 25% | 25% | | > 1.06 (0.52 to 2.14) | | |
| <60y, Recent | 50% | 36% | | 0.63 (0.39 to 1.01) | | |
| >=60y, Chronic | 17% | 20% | _ | → 1.12 (0.45 to 2.76) | | |
| >=60y, Recent | 33% | 26% | | 0.69 (0.37 to 1.29) | | |
| | | | 0 1 | 2 | | |
| | | ÷⊤ | reatment Better Placebo Bet | | | |
| l reatment Better Placebo Better | | | | | | |
| | | 1 | | | | |
| Subgroup | Placebo (N = 261) | Valacyclovir (N = | 266) | HR (adjusted 95% Cl) | | |
| Subgroup Sex | Placebo (N = 261) | Valacyclovir (N = | 266) | HR (adjusted 95% CI) | | |
| Subgroup Sex Male | Placebo (N = 261) | Valacyclovir (N = | 266) | HR (adjusted 95% Cl) | | |
| Subgroup Sex Male Female | Placebo (N = 261) 42% 38% | Valacyclovir (N = 39% 26% | 266) | HR (adjusted 95% Cl) 0.88 (0.6 to 1.29) 0.62 (0.4 to 0.97) | | |
| Subgroup Sex Male Female Strata | Placebo (N = 261) 42% 38% | Valacyclovir (N = 39% 26% | 266) | HR (adjusted 95% CI) 0.88 (0.6 to 1.29) 0.62 (0.4 to 0.97) | | |
| Subgroup Sex Male Female Strata <60y, Chronic | Placebo (N = 261) 42% 38% 30% | Valacyclovir (N = 39% 26% 35% | 266) | HR (adjusted 95% CI) 0.88 (0.6 to 1.29) 0.62 (0.4 to 0.97) → 1.2 (0.64 to 2.25) | | |
| Subgroup Sex Male Female Strata <60y, Chronic <60y, Recent | Placebo (N = 261) 42% 38% 30% 53% | Valacyclovir (N = 39% 26% 35% 41% | 266) | HR (adjusted 95% CI) 0.88 (0.6 to 1.29) 0.62 (0.4 to 0.97) → 1.2 (0.64 to 2.25) 0.66 (0.42 to 1.05) | | |
| Subgroup Sex Male Female Strata <60y, Chronic <60y, Recent >=60y, Chronic | Placebo (N = 261) 42% 38% 30% 53% 33% | Valacyclovir (N = 39% 26% 35% 41% 22% | 266) | HR (adjusted 95% Cl) 0.88 (0.6 to 1.29) 0.62 (0.4 to 0.97) → 1.2 (0.64 to 2.25) 0.66 (0.42 to 1.05) 0.64 (0.3 to 1.36) | | |
| Subgroup Sex Male Female Strata <60y, Chronic <60y, Recent >=60y, Recent | Placebo (N = 261) 42% 38% 30% 53% 33% 40% | Valacyclovir (N = 39% 26% 35% 41% 22% 27% | 266) | HR (adjusted 95% Cl) 0.88 (0.6 to 1.29) 0.62 (0.4 to 0.97) → 1.2 (0.64 to 2.25) 0.66 (0.42 to 1.05) 0.64 (0.3 to 1.36) 0.61 (0.34 to 1.1) | | |

Treatment Better Placebo Better





Statistical Analysis of Benefit in Each of Four Strata

p values for the HRs, adjusted 95 percent confidence intervals (CIs)

Suggestion of benefit in pre-specified analysis

- At 12 months <60, Recent onset: p = 0.06 [HR: 0.63, (95 percent CI 0.39-1.01)]
- At 18 months <60, Recent onset: **p = 0.08** [**HR: 0.66**, (95 percent CI 0.42-1.05)]
 - But Cochran Q tests indicated no significant heterogeneity of treatment effects across the four strata

Comments

- HR: 0.63 means 37 percent reduction
- p < 0.05 statistically significant
 - But does not measure importance of result or provide good evidence of measure regarding hypothesis, shift focus to clinical relevance—magnitude of result with confidence intervals
 - Nead KT JAMA Oncol. 2018 Dec; 4(12): 1778–1779





Valacyclovir Treatment Benefit for Recent Onset HZO (Enrolled within 6 months)

Analysis by combining recent onset strata (not pre-specified) showed significant reduction in endpoints in recent onset HZO

- 12 months HR = 0.65, adjusted 95 percent CI: 0.45-0.96, p = 0.03
- 18 months HR = 0.64, adjusted 95 percent CI 0.45-0.92, p = 0.02

Comments

- In Statistical Analysis Plan (SAP) hypothesized that treatment benefit greater in recent onset
- · Consider clinically meaningful in guiding care





Subsequent Endpoints by Treatment Group

Note: Participants had at least one episode for eligibility, primary endpoint at least second episode, and subsequent endpoint at least third

| | Total | Placebo | Valacyclovir | | Total | Placebo | Valacyclovir |
|--------------------------------|-----------|-----------|--------------------------------|-----|-----------|--------------|--------------|
| | (N=527) | (N=261) | (N=266) | | (N=527) | (N=261) | (N=266) |
| Primary endpoint | | | Primary endpoint | | | | |
| No | 367 (70%) | 175 (67%) | 192 (72%) | No | 336 (64%) | 157 (60%) | 180 (68%) |
| Yes | 160 (30%) | 86 (33%) | 74 (28%) | Yes | 190 (36%) | 104 (40%) | 86 (32%) |
| Number of subsequent endpoints | | | Number of subsequent endpoints | | | | |
| 0 | 122 (23%) | 61 (23%) | 61 (23%) | 0 | 134 (25%) | 70 (27%) | 63 (24%) |
| 1 | 26 (5%) | 15 (6%) | 11 (4%) | 1 | 39 (7%) | 21 (8%) | 18 (7%) |
| 2 | 4 (1%) | 3 (1%) | 1 (0%) | 2 | 10 (2%) | 6 (2%) | 4 (2%) |
| 3 | 6 (1%) | 6 (2%) | 0 (0%) | 3 | 6 (1%) | 6 (2%) | 0 (0%) |
| 4 | 1 (0%) | 0 (0%) | 1 (0%) | 4 | 0 (0%) | 0 (0%) | 0 (0%) |
| 5 | 1 (0%) | 1 (0%) | 0 (0%) | 5 | 2 (0%) | 1 (0%) | 1 (0%) |
| By 12 months | | | | | I | By 18 months | |





Significant Valacyclovir Treatment Benefit in Reducing Subsequent Endpoints

Participants randomized to valacyclovir had a significantly lower HR of experiencing subsequent endpoints compared to those on placebo.

- At 12 months: HR: 0.69, adjusted 95 percent CI 0.51-0.94, p = 0.02
- At 18 months: HR: 0.71, adjusted 95 percent CI 0.54-0.94, **p = 0.02**





ZEDS Guidance for Evidence-Based Clinical Practice

- Evidence supports suppressive valacyclovir treatment 1000 mg daily for one year to reduce new or worsening keratitis or iritis in immunocompetent, non-pregnant adults with good renal function
 - Pre-specified analysis of primary endpoint did not show overall significant benefit at 12 months but did at 18 months (secondary endpoint)
- Evidence supports suppressive valacyclovir treatment to reduce multiple episodes of keratitis or iritis at 12 and 18 months





Second Aim: Postherpetic Neuralgia

- Zoster Brief Pain Inventory (ZBPI) score of worst pain in last 24 hours of 3/10 or more occurring 3 or more months after HZO onset was used to determine the prevalence, severity, and duration of PHN
- The effect of valacyclovir treatment on medication usage for pain was also analyzed
- At enrollment 73 (73/527, 14 percent) participants had PHN
 - -Valacyclovir: 34 Placebo: 39
- PHN was significantly more common in participants with HZO onset age 60 or older (48/241, 20 percent, p = 0.007)
 - -But PHN also occurred in younger participants (25/286, 9 percent).





Participants with PHN at Enrollment

- Prevalence not reduced overall
- Participants <60 years at HZO onset on valacyclovir had a significantly lower prevalence of PHN at 18 months (p = 0.05)
 - 12 and 18 months in specific aim for PHN are both equal secondary objectives
 - Combined strata analysis by age ad hoc, not pre-specified







Pain Scores

- Participants in the <60 year-onset chronic stratum on valacyclovir had significantly lower pain scores at 12 and 18 months (p = 0.045, p = 0.020)
- Participants on valacyclovir in the ≥60 year chronic stratum had a suggestion of greater decrease in pain at 18 months (p = 0.07)







Pain Duration

Among all participants, there was a **significant decrease** in pain duration for those on valacyclovir compared to placebo at **18 months** [difference of -3.39 (Cl -6.73, -0.04), **p = 0.05**]







Change in Dose of Neuropathic Pain Medications

- There was a statistically significant reduction in the dose of neuropathic medications at 12 and 18 months (p = 0.006 and p = 0.012, respectively) for participants on valacyclovir
- This was a pre-specified analysis with significant benefit across strata at both times!







ZEDS Guidance for Evidence-Based Treatment of PHN/Pain

Recommend 1 year of suppressive valacyclovir in HZO patients

• HZO Onset < 60 years, chronic stratum

-Significantly lower pain scores at <u>12</u> (p = 0.05), <u>18</u> months (p = 0.02)

- HZO Overall
 - -Significant decrease in pain duration at <u>18</u> months (p = 0.05)

Why is benefit greater at 18 months? Speculation: takes injured nerves time to heal??





ZEDS Guidance for Evidence-Based Treatment of PHN

Recommend one year of suppressive valacyclovir to significantly reduce dose of neuropathic pain medications at 12 and 18 months (p = 0.006, p = 0.012)

Comments

- Valacyclovir safe and well tolerated compared to neuropathic pain medications
- Treatment benefits for pain due to zoster in other locations merit study





Gratitude

- 14-year journey from idea to results
- 6 years of planning and 3 grant applications to secure funding from NEI
 - -Tremendous support from across NYULH
- 8-year study
 - -Continued huge NYULH support
 - -Enrollment at 82 centers in 3 countries; many thanks to PIs, Co-Is, and coordinators for their hard work, persistence, and dedication
 - -Special appreciation for study participants who volunteered
 - -Invaluable support from NEI and the National Shingles Foundation
- Achieved aims of developing high-quality evidence-based guidance for use of suppressive valacyclovir to improve outcomes in HZO and PHN/pain that will benefit many patients





Recombinant Zoster Vaccine (RZV. Shingrix)

Lal H et al. N Engl J Med 2015; 372:2087-96. Cunningham N Engl J Med 2016; 375:1019-32

- Adjuvanted herpes zoster subunit vaccine (GlaxoSmithKline)
 - Recombinant VZV glycoprotein E antigen, novel AS01B adjuvant
- ZOE-50 RCT in immunocompetent adults age 50 years and older
 - 2 IM injections 2 months apart of vaccine or saline placebo
 - Results: ~97 percent efficacy for all age groups
 - Grade 3 severe acute symptoms interfering with activities in 17 percent
- Vaccine efficacy pooled in 2 ZOE-70, ZOE-50 trials
- Results: efficacy: ~90 percent in vaccine recipients age 70s and 80s
- Efficacy against HZ persists: 85 % year 4, **73% year 10,** CD4 T-cell stable >6x vs pre vax yr 5-10 Strezova et al Open Forum Infectious Dis. 2022; 9:ofac485
- FDA-approved Recombinant Zoster Vaccine (RZV) October 2017, age 50+
- CDC recommended January 26, 2018, MMWR for immunocompetent 50+



RZV in Immunocompromised: FDA Approval and CDC Recommendations

FDA approval July 2021

Adults age 18+ who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or treatment

CDC recommendations January 2022

- Anderson TC, Masters NB, Guo A et al. MMWR 2022; 71:80-84
- Recommends 2 RZV doses for immunodeficient or immunosuppressed age 19 years+
- 2 doses 2–6 months apart, but can be 1–2 months apart
- Timing: before immunosuppressed, or when immune response is best
- Give if they've gotten the varicella vaccine
- Can be on antivirals
- At same time/different site as other vaccinations, including COVID-19
- For persons with hx of HZ





Recent Publications on Possible Benefits of HZ Vaccination

- Association of HZ and flu vaccinations with risk of dementia: a population-based cohort study within the UK (ZVL 2013-2020 for age 70-80)
 - HZ vaccination lowers risk of dementia: HR 0.78 (95 percent CI 0.77-0.79) vs. flu HR 0.96
- Causal Evidence HZ Vaccination prevents proportion of dementia (pre-print)
 - -Wales: study compared born 1 week before vs. 1 week after cut-off 80-year olds for ZVL in 2013
 - Decreased risk over 7 years by 3.5 percent, p = 0.019, 19.9 percent relative reduction in dementia
 - Lophatananon A BMC Public Health 2023; 23:1903. Eyting M medRxiv 2023 May 25
- Recombinant Zoster Vaccine (RZV) and Risk of Dementia (Tang E Vaccine online 28 Dec 2024)
 - Retrospective cohort study of USA claims data on 4.5 million persons, 5 yrs maximum follow-up
 - -2 doses decreased risk dementia: hazard ratio (HR) 0.68, P < .001; 1 dose: HR 0.89, P < .001
 - N with 2 doses RZV was 45 to prevent 1 dementia
 - Diagnosis zoster pre vax: increased HR dementia: 1.47, P < .001
 - Antiviral treatment decreased HR dementia: 0.42, P < .001 if for zoster, 0.59, P < .001 for other dx





Case

A healthy person in her 50s developed unilateral radicular thoracic pain and a rash 1 week later. Treatment for HZ was begun; next day had leg numbness and weakness with transverse myelitis due to HZ. At 1 year, still had PHN with constant 5/10 pain, and 8 years later, pain and difficulty walking

Lessons

- Can't predict who will have serious complications of HZ!
 - Non-PHN complications as common in younger patients as older
- Recommend vaccination against HZ at age 50+!!





Update on Zoster Vaccination

- CDC Surveillance Vaccination Coverage among Adults (MMWR <u>2021;</u> 70:1-26) <u>2018</u>: ZVL: 3.7 percent age 50–59, 28 percent age 60+; RZV: 0.6 percent age 50+
- National Health Interview Survey 2021 (CDC.gov/vaccines AdultVaxView)
 RZV: 12.2 percent age 50–59, 22 percent age 60+
- Vaccine co-administration in adults: An effective way to improve coverage (Bonanni P Hum Vaccin Immunother. 2023; 19:21957856)
- Effectiveness of RZV in Real-World Setting (Zerbo O. Ann Intern Med 9 Jan 2024)
 2 million age 50+ in Vaccine Safety Datalink, HZ dx, and antiviral rx
 2 doses: 76 percent effective, 73 percent 4th year; 1 dose: 64 percent effective, 52 percent yr 3

Conclusions:

- 2 dose series is important for long-term efficacy, but second dose can be delayed
- Need to improve coverage of RZV starting at age 50 and for immunocompromised starting at 19 – MDs need to strongly recommend it!
- <u>Importance of a moral obligation to do the right thing to change behavior</u> (Arthur Caplan, PhD, talk on flu vaccination) NYU Grossman School of Medicine



Thank you

Elisabeth.Cohen@nyulangone.org

