Published in final edited form as:

J Rheumatol. 2017 July ; 44(7): 1083–1087. doi:10.3899/jrheum.160685.

Long term effectiveness of herpes zoster vaccine among patients with autoimmune and inflammatory diseases

Huifeng Yun, PhD, Fenglong Xie, MS, John W Baddley, MD, MPH, Kevin Winthrop, MD, MPH, Kenneth Saag, MD, MSc, and Jeffrey Curtis, MD, MS, MPH

Abstract

Background—The protection duration of herpes zoster (HZ) vaccination is unclear among patients with autoimmune (AI) diseases.

Methods—Using 2006–2013 Medicare data, HZ vaccinated AI patients were matched 1:2 to HZ unvaccinated. Incidence rates (IRs) and adjusted risk ratios over time were calculated using Poisson regression.

Results—Of 59,627 vaccinated patients, crude IRs increased from 0.75/100 person years during the first year post vaccination to 1.25 during the 7th year. Vaccinated patients had a significantly lower risk of HZ compared to the unvaccinated through 5 years.

Conclusion—HZ vaccination was significantly protective only for approximately 5 years among AI patients.

INTRODUCTION

The pain caused by Herpes zoster (HZ), also known as shingles, is sometimes severe and may have a major impact on quality of life (1, 2). Although antiviral treatment of HZ can reduce the severity and duration of HZ, it may not prevent post-herpetic neuralgia (3). To prevent HZ and post-herpetic neuralgia, the U.S. Center for Disease Control (CDC) recommended the live HZ vaccine (Zostavax) for healthy adults age 60 years and older in 2006 (4).

The Shingles Prevention Study (SPS) showed that HZ vaccine reduced the incidence of HZ by 51% and remained efficacious through several years of post-vaccination among immunocompetent patients (5, 6). In long-term follow-up of SPS participants, zoster vaccination was shown to lose most of its protective benefit over 10 years (7). Although observational studies have reported that HZ vaccine significantly reduce HZ and post-herpetic neuralgia in patients with autoimmune or inflammatory (AI) conditions (8, 9).

Corresponding Author: Jeffrey R. Curtis, MD MS MPH, 510 20th Street South, Faculty Office Towers 802D, Birmingham, AL 35294, jcurtis@uab.edu, Phone: 205-975-2176.

Disclosures

Yun: Research grants: Amgen

Baddley: consulting for Eli Lilly, Pfizer and research grants from BMS

Winthrop: research grants: Pfizer, Inc/consulting fees: Pfizer, UCB, Genentech, Regeneron, Genentech, Merck, Takeda

Saag: research grants: Amgen, Ardea, Takeda/Consulting fees: Amgen Ardea, Astra Zeneca Bayer

Curtis: research grants and/or consulting: Amgen, BMS, Crescendo, CORRONA, Lilly, Pfizer, Janssen, UCB

However the duration of protection among AI patients, who might have an attenuated vaccine response due to immune suppression, is unclear. Therefore, we evaluated the duration of HZ vaccine effectiveness among older AI patients.

METHODS

Data sources and study design

Using 2006–2013 Medicare data, we conducted a retrospective cohort study among 100% of patients with AI diseases, including rheumatoid arthritis (RA), ankylosing spondylitis (AS), inflammatory bowel disease (IBD), psoriasis (PSO), and psoriatic arthritis (PsA). Medicare is the U.S. health insurance program for people age 65 or older and for younger people with disabling conditions (e.g. RA). Medicare data include information on diagnoses, procedures, hospitalizations, physician visits and prescriptions. Both Medicare and the Institutional Review Board of the University of Alabama at Birmingham approved the study X121029003.

Study population and eligible criteria

After patients with RA (714.x), AS (720.0x), IBD (555.x, 556.x), PSO (696.1x) or PSA (696.0x) were identified using 2 physician ICD9 diagnosis codes (10), we identified patients who had HZ vaccinations using current Procedural terminology (CPT) code 90736 or National Drug Codes (NDC). The vaccination date was determined as the CPT code date or the NDC date if no corresponding CPT was found within 7 days after the NDC date.

Eligible patients were required to have 12 months continuous Medicare fee for service coverage (baseline) before vaccination and throughout follow up. We excluded patients with ICD9 diagnosis codes or prescriptions for HZ during baseline. Vaccinated patients were matched 1:2 to unvaccinated on calendar year, age, gender, race, AI disease, and use of biologics, DMARDs and glucocorticoids. Biologic and DMARDs were categorized as dichotomous, whereas the average glucocorticoid prednisone-equivalent dose during the 6 months before vaccination was categorized as none, <7.5 mg/day, and ≥7.5 mg/day. To understand long term effectiveness and avoid misclassification related to healthcare associated with vaccine administration, follow-up started from 30 days after the vaccination date or corresponding calendar date in the matched cohort, and ended at the earliest of first HZ, death, loss of coverage or 12/31/2013. Matched patients were censored if they were subsequently vaccinated, and then included in the vaccination group and re-matched. The maximum follow-up time was 7 years post-vaccination.

Outcome

The outcome was first HZ event during follow-up. We identified HZ using an ICD-9 inpatient diagnosis code alone(053.x) or an outpatient diagnosis code plus antiviral medication(famciclovir, acyclovir, valacyclovir) within 7 days of HZ diagnosis. This previously-validated algorithm has high positive predictive value (PPV ≥85%)(11, 12).

Potential confounders

Besides matching factors, we evaluated other potential confounders including baseline medical conditions and concurrent medications, and updated them in each follow-up year. Medical conditions include diabetes, chronic obstructive pulmonary disease (COPD), renal disease, heart failure and outpatient infections. Concurrent medications included narcotics, anti-depressive drugs and nonsteroidal anti-inflammatory drugs (NSAIDs).

Statistical analysis

We conducted descriptive analysis for potential confounders by HZ vaccination status. We calculated incidence rates (IRs) for each year of post-vaccination stratified by whether patients were vaccinated or not. Using matched, un-vaccinated patients as referent (13, 14), conditional Poisson regression for repeated measures was applied to calculate the adjusted risk ratio of HZ each year of post-vaccination controlling for matched variables and additional potential confounders. Analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC).

Sensitivity and subgroup analyses

We conducted a sensitivity analysis that identified HZ only using inpatient or outpatient diagnosis codes (053.x) without requiring anti-viral drug use. We conducted subgroup analyses to evaluate HZ vaccine effectiveness stratified by age (<70 and ≥70) and glucocorticoid dose category.

RESULTS

The vaccinated cohort consisted of 59,627 patients, whereas the matched unvaccinated cohort included 119,254 patients. The factors on which patients were matched were balanced as expected (Table 1). Mean age in both groups was 73.7; 46.5% of the cohort had rheumatoid arthritis, 31.7% psoriasis, 4.5% psoriatic arthritis, 21.1% inflammatory bowel disease, and 1.4% ankylosing spondylitis.

As Figure 1 shown, HZ IRs in the vaccinated group increased from 0.75 per 100 person years (PYs) in the 1st year post vaccination to 1.25 in the 7th year post vaccination. In contrast, the HZ IRs among unvaccinated remained relatively constant (1.3 to 1.7/100PYs) through 7 years of follow-up. After adjusting for matched variable and potential confounders (all in table one), vaccinated patients had significantly lower risk of HZ compared to unvaccinated patients over 5 years. The relative risk for HZ during years 3–5 ranged from 0.74–0.77, and the upper bound of the 95% CI ranged from 0.87 to 0.97. This protective effect was not significant during the 6th and 7th year after vaccination (Figure 2).

Both sensitivity analyses that did not require HZ treatment yielded similar results as our main analysis and subgroup analyses that stratified by patient's age and glucocorticoid dosage categories yielded consistent trends with the main analysis (not shown).

DISCUSSION

There has been some concern that patients with AI conditions might have a lower immunogenic response to HZ vaccination, especially when treated with immune-suppressive medications such as glucocorticoids (15, 16). Reassuringly, we found that in older patients with autoimmune diseases, the HZ vaccine was effective in the short term, and that its effectiveness waned over time. HZ risk was most reduced in the first year post-vaccination and increased back to the unvaccinated rate over approximately 5–7 years.

The attenuating effectiveness over time of HZ vaccination observed in our analysis have been reported in the general population, although in healthy older people, the protection associated with vaccination appears to last somewhat longer. A previous analysis reported the vaccine efficacy declined after first year post vaccination but remained significantly protective for at least 5 years (6). Likewise, the subsequently published Long Term Persistence Substudy (LTPS) showed that vaccine effectiveness continued to decline, but remained statistically significant through year 8 post vaccination (7). In addition, an observational study conducted among healthy older members of Kaiser Permanente Northern California (KPNC) in 2007–2013 also found the HZ vaccine effectiveness in routine use waned over time. In that observational analysis, the protective effects of vaccination remained significant over seven years following vaccination (17). Our study found that HZ vaccination was significantly protective in the short term. The non-significant effectiveness during the 6–7th years of post-vaccination may be due to small numbers, but the effect estimates of the vaccine's benefit by year 7 were negligible (IRR 0.96), irrespective of the 95% confidence intervals.

As expected, our study conducted in patients with autoimmune diseases had higher absolute incidence rates of HZ in each post-vaccination year than those reported in the general population. In unvaccinated healthy older people in the SPS, the absolute IR was 1.1 per 100py in patients age 70 and older. Rates in our study were approximately 50% increased, consistent with prior observations that have found elevated rates of HZ in autoimmune disease patients (18).

Unlike randomized trials, this observational study lacked detailed information on disease activity and clinical factors, and thus residual confounding is possible. Although the claims-based algorithm for HZ has been shown to have good PPV, medical records were not available to confirm HZ, so misclassification was possible, although unlikely to be differential by vaccination status. Additionally, misclassification of HZ vaccination was possible if individuals paid for their vaccination without using insurance coverage. However, because all patients were required to have full coverage and given the expense of the vaccine (>\$200), vaccination administration not captured by Medicare should have been rare. Finally, the insignificant effectiveness during the 6–7th years may be due to the limited events and person time, however, the clinical benefits in these two years are limited as well as the reported risk ratio estimates were close to one,

In conclusion, the duration of HZ vaccine effectiveness waned over approximately 5 years among older patients with AI conditions, many of whom were on immunosuppressive and

immunomodulatory agents. This finding raises the possibility that patients might benefit from a booster vaccine at some point after initial vaccination, although no recommendation currently exists that would support such a practice. Further research is needed to determine when and if such a strategy is effective.

References

1. Cohen JI. Herpes zoster. *N Engl J Med*. 2013; 369:1766–7.
2. Langan SM, Smeeth L, Margolis DJ, Thomas SL. Herpes zoster vaccine effectiveness against incident herpes zoster and post-herpetic neuralgia in an older US population: a cohort study. *PLoS medicine*. 2013; 10:e1001420. [PubMed: 23585738]
3. Dworkin RH, Schmader KE. Treatment and prevention of postherpetic neuralgia. *Clin Infect Dis*. 2003; 36:877–82. [PubMed: 12652389]
4. CDC. Prevention of Herpes Zoster. Morbidity and Mortality Weekly Report 2008. *MMWR Early Release*. 2008;57.
5. Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med*. 2005; 352:2271–84. [PubMed: 15930418]
6. Schmader KE, Oxman MN, Levin MJ, Johnson G, Zhang JH, Betts R, et al. Persistence of the efficacy of zoster vaccine in the shingles prevention study and the short-term persistence substudy. *Clin Infect Dis*. 2012; 55:1320–8. [PubMed: 22828595]
7. Morrison VA, Johnson GR, Schmader KE, Levin MJ, Zhang JH, Looney DJ, et al. Long-term persistence of zoster vaccine efficacy. *Clin Infect Dis*. 2015; 60:900–9. [PubMed: 25416754]
8. Zhang J, Xie F, Delzell E, Chen L, Winthrop KL, Lewis JD, et al. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. *JAMA*. 2012; 308:43–9. [PubMed: 22760290]
9. Zhang J, Delzell E, Curtis JR. Postherpetic Neuralgia after Herpes Zoster Vaccination-Reply. *JAMA*. 2012; 308:1427–8. [PubMed: 23047346]
10. Herrinton LJ, Curtis JR, Chen L, Liu L, Delzell E, Lewis JD, et al. Study design for a comprehensive assessment of biologic safety using multiple healthcare data systems. *Pharmacoepidemiol Drug Saf*. 2011; 20:1199–209. [PubMed: 21919113]
11. Donahue JG, Choo PW, Manson JE, Platt R. The incidence of herpes zoster. *Arch Intern Med*. 1995; 155:1605–9. [PubMed: 7618983]
12. Mullooly JP, Riedlinger K, Chun C, Weinmann S, Houston H. Incidence of herpes zoster, 1997–2002. *Epidemiology and infection*. 2005; 133:245–53. [PubMed: 15816149]
13. Farrington CP. Relative incidence estimation from case series for vaccine safety evaluation. *Biometrics*. 1995; 51:228–35. [PubMed: 7766778]
14. Cameron, AC., Trivedi, PK. Regression analysis of count data. New York: NY: Cambridge University Press; 1998.
15. Adler S, Krivine A, Weix J, Rozenberg F, Launay O, Huesler J, et al. Protective effect of A/H1N1 vaccination in immune-mediated disease--a prospectively controlled vaccination study. *Rheumatology*. 2012; 51:695–700. [PubMed: 22171015]
16. Bingham CO 3rd, Looney RJ, Deodhar A, Halsey N, Greenwald M, Coddling C, et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: results from a controlled clinical trial. *Arthritis Rheum*. 2010; 62:64–74. [PubMed: 20039397]
17. Tseng HF, Harpaz R, Luo Y, Hales CM, Sy LS, Tartof SY, et al. Declining Effectiveness of Herpes Zoster Vaccine in Adults Aged ≥ 60 Years. *J Infect Dis*. 2016; 213:1872–5. [PubMed: 26908728]
18. Yun H, Yang S, Chen L, Xie F, Winthrop K, Baddley JW, et al. Risk of Herpes Zoster in Autoimmune and Inflammatory Diseases: Implications for Vaccination. *Arthritis & rheumatology*. 2016; 68:2328–37. [PubMed: 26990731]

Vaccinated	year 1	year 2	year 3	year 4	year 5	year 6	year 7
Events	328	315	225	169	120	74	11
Person Years	44472	30939	20308	14718	9178	5381	877
IR per 100	0.74	1.02	1.11	1.15	1.31	1.38	1.25
Not vaccinated							
Events	1138	819	514	347	229	117	19
Person Years	86149	57855	34490	22847	13405	7245	1411
IR per 100	1.32	1.42	1.49	1.52	1.71	1.61	1.35

Figure 1.
Incidence rate (IR) and 95% Confidence Interval for herpes zoster over time among vaccinated patients compared to the matched unvaccinated patients

Figure 2.
Adjusted risk ratio (RR) of herpes zoster by years of post-vaccination compared to the matched unvaccinated patients

Table 1

Baseline characteristics for the vaccinated cohort and matched non-vaccinated cohort

	Vaccinated cohort N=59,627	Non-vaccinated cohort N=119,254
Matched Variables		
Age, Mean (STD)	73.5 (7.3)	73.5 (7.3)
Female Sex	69.7	69.7
Race		
White	93.1	93.1
Black	2.9	2.9
Asian	1.6	1.6
Hispanic	1.0	1.0
Other	1.5	1.5
Index year of vaccination or start of follow-up		
2007	6.8	6.8
2008	8.3	8.3
2009	12.1	12.1
2010	7.5	7.5
2011	11.9	11.9
2012	25.9	25.9
2013	27.6	27.6
Autoimmune disease, %		
RA	53.1	53.1
AS	1.4	1.4
IBD	20.9	20.9
PSO	31.6	31.6
PSA	4.7	4.7
Any biologic use prior to index date, %	11.0	11.0
Disease modifying anti-rheumatic drugs, %	46.1	46.1
Glucocorticoids		
None	83.5	83.5
<7.5 mg/day	14.0	14.0
7.5 mg/day	2.5	2.5
Variables not matched on		
Diabetes	26.7	22.3
Chronic obstructive pulmonary disease	24.9	21.0
Renal disease	10.4	8.5
Heart failure	11.3	7.3
Outpatient Infection during baseline	44.8	42.9
Narcotics	50.7	47.4

	Vaccinated cohort N=59,627	Non-vaccinated cohort N=119,254
Anti-depressive	27.7	26.2
Nonsteroidal anti-inflammatory drugs	21.8	23.5

Data shown as % unless otherwise indicated