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Association Between Vaccination for Herpes Zoster and Risk of Herpes Zoster Infection Among Older Patients With Selected Immune-Mediated Diseases

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Context Based on limited data, the live attenuated herpes zoster (HZ) vaccine is contraindicated in patients taking anti–tumor necrosis factor (anti-TNF) therapies or other biologics commonly used to treat immune-mediated diseases. The safety and effectiveness of the vaccine are unclear for these patients.

Objective To examine the association between HZ vaccination and HZ incidence within and beyond 42 days after vaccination in patients with selected immune-mediated diseases and in relation to biologics and other therapies used to treat these conditions.

Design, Setting, and Patients Retrospective cohort study of 463 541 Medicare beneficiaries 60 years and older with rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, or inflammatory bowel disease using Medicare claims data from January 1, 2006, through December 31, 2009.

Main Outcome Measures Herpes zoster incidence rate within 42 days after vaccination (a safety concern) and beyond 42 days; hazard ratios estimated using Cox proportional hazards models for HZ comparing vaccinated vs unvaccinated patients.

Results Median duration of follow-up was 2.0 years (interquartile range, 0.8-3.0); 4.0% of patients received HZ vaccine. The overall crude HZ incidence rate was 7.8 cases per 1000 person-years (95% CI, 3.7-16.5) within 42 days after vaccination. The rate among the unvaccinated was 11.6 cases per 1000 person-years (95% CI, 11.4-11.9). Among 633 patients exposed to biologics at the time of vaccination or within the subsequent 42 days, no case of HZ or varicella occurred. After multivariable adjustment, HZ vaccination was associated with a hazard ratio of 0.61 (95% CI, 0.52-0.71) for HZ risk after 42 days.

Conclusions Receipt of HZ vaccine was not associated with a short-term increase in HZ incidence among Medicare beneficiaries with selected immune-mediated diseases, including those exposed to biologics. The vaccine was associated with a lower HZ incidence over a median of 2 years of follow-up.

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HERPES ZOSTER (HZ), CAUSED by the reactivation of latent varicella-zoster virus (VZV), manifests as an acute, painful vesicular rash and is often accompanied by chronic pain or postherpetic neuralgia.[1] In the United States, the incidence rate of HZ in the unvaccinated general population 50 years or older is estimated to be 7.0 cases per 1000 person-years.[2] A live attenuated vaccine reduces HZ risk by 70% and 51% among immunocompetent individuals 50 to 59 years and 60 years and older in 2 randomized blinded trials, respectively.[3,4] The Advisory Committee on Immunization Practices (ACIP) recommends a single dose of the zoster vaccine for all people 60 years or older.[5]

The risk of HZ is elevated by 1.5 to 2 times in patients with rheumatic and immune-mediated diseases such as rheumatoid arthritis (RA) and Crohn disease.[6-9] This increase has been attributed to both the underlying disease process and treatments for these conditions.[6,8-10] Currently, the Food and Drug Administration (FDA), the ACIP, and the American College of Rheumatology consider the live HZ vaccine to be contraindicated in patients receiving some immunosuppressive medications commonly used to treat these conditions, including all immune-modulating biologic agents;

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some nonbiologic immunosuppressive medications, such as methotrexate at doses of greater than 0.4 mg per kg per week; and glucocorticoids at prednisone-equivalent doses of 20 mg or more per day.[11,12] The safety concern is that these individuals may develop varicella infection from the vaccine virus strain. Based on the VZV incubation period,[13,14] the first 42 days following vaccination was chosen as the primary safety risk window in the Shingles Prevention Study, a randomized blinded trial that preceded the FDA approval of the vaccine.[4]

In light of the uncertainties regarding the safety and effectiveness of zoster vaccine in patients with immune-mediated diseases, we used administrative claims from US Medicare beneficiaries diagnosed with these diseases to evaluate the association between receipt of zoster vaccine and HZ risk within the first 42 days and up to 3.5 years following vaccination.

METHODS

The study was a retrospective cohort analysis conducted among Medicare beneficiaries diagnosed with RA, psoriatic arthritis, psoriasis, ankylosing spondylitis, or inflammatory bowel disease (Crohn disease or ulcerative colitis) using medical and pharmacy claims data from January 1, 2006, through December 31, 2009, a period during which zoster vaccine was approved for use among individuals 60 years or older. Eligible patients had to satisfy the following 3 criteria: (1) to be at least 60 years of age; (2) to have a diagnosis of at least 1 of the above diseases established by having at least 2 physician diagnosis codes that were at least 7 days apart but less than 12 months apart; and (3) to have at least 6 months of continuous enrollment in Medicare Part A, Part B, and Part D but not in a Medicare Advantage Plan. These coverage requirements ensured a complete claims history for each eligible beneficiary for services received in inpatient, outpatient, and emergency department settings and prescriptions filled in outpatient settings.

For all eligible patients, follow-up started on the earliest date (defined as the index date) a patient satisfied the 3 criteria. The 6 months immediately prior to the index date was defined as the baseline period. Follow-up ended when an outcome (HZ) occurred; the patient lost Part A, Part B, or Part D coverage or entered a Medicare Advantage plan; the patient died; or on December 31, 2009. Patients who had an HZ diagnosis during the 6-month baseline period were excluded from the analysis to ensure the identification of incident, rather than prevalent, cases of HZ. Race in Medicare is derived from the Social Security Administration's records and is self-reported when beneficiaries apply for a Social Security number.

Medication Exposure

Follow-up time was categorized on a person-day basis with regard to medication exposure. The 4 groups of medications of interest were as follows: anti–tumor necrosis factor (TNF) biologics (adalimumab, etanercept, infliximab, certolizumab, and golimumab), non-TNF biologics (abatacept and rituximab), nonbiologic immunosuppressive medications (or disease-modifying antirheumatic drugs [DMARDs]) (methotrexate, hydroxycholoroquine, sulfasalazine, azathioprine, leflunomide, cyclosporine, and 6-mercaptopurine), and oral glucocorticoids. Exposure to biologics and nonbiologic DMARDs was determined based on prescription date and days of supply and, for infusions, the recommended dosing intervals. For example, a patient who received an infliximab infusion was considered exposed to infliximab for the next 56 days from the infusion date. Because the exact daily dose of oral glucocorticoids is challenging to ascertain in these types of data, a patient was considered exposed to oral glucocorticoids if the patient received any oral glucocorticoids in the previous 90 days (vs none).

Unless explicitly stated, the use of combination medications was categorized into mutually exclusive groups based on the following hierarchy: (1) any anti-TNF biologics, (2) any non-TNF biologics, (3) any nonbiologic DMARDs, and (4) any oral glucocorticoids.

HZ Vaccination

The administration of zoster vaccine was identified by Current Procedural Terminology (CPT) code 90736; or a combination of the National Drug Code (NDC) for the zoster vaccine (representing the purchase of the vaccine) followed by either the Health Care Common Procedure Coding System (HCPCS) code G0377 or the CPT code 90471 in the subsequent 7 days (representing its administration). The vaccination administration date was defined as the date when the vaccine injection procedure was identified.

For some patients, there was record of the patient having purchased the zoster vaccine but no procedure code identifying the exact date of administration, perhaps because remuneration for simply administering the vaccine is low and thus the claim was not submitted or because administration cost and vaccine cost could be billed on 1 claim after 2008. Because the exact vaccination administration date was not known for these patients, and an HZ or varicella diagnosis code appearing shortly after the purchase date might be associated only with the administration of the vaccine but not HZ, the first 42 days following vaccine purchase for these patients were excluded from the safety analysis. These patients did contribute person-time before and after 42 days to the effectiveness analysis. A sensitivity analysis was performed in which patients without known vaccine administration dates were censored at time of vaccine purchase.

Case Definition of HZ Infection

Incident HZ cases were identified by the first HZ diagnosis code occurring during follow-up (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] code 053) in an inpatient or physician office visit

claim that was accompanied by a pharmacy claim for antiviral treatment (acyclovir, famciclovir, valacyclovir) within 7 days before or after. Because this case definition relied on the assumption that the antiviral treatment was intended for the treatment of HZ, patients exposed to the antiviral treatment in the 6-month baseline period were excluded from the analysis. The positive predictive value (PPV) of the HZ diagnosis code alone to identify a new case of HZ (using medical record review as a gold standard) has been shown to range between 85% and 100%.[15,16] The additional requirement for antiviral drug use was applied to further improve the PPV to better distinguish incident HZ from a history of, or prevalent, HZ. In a sensitivity analysis, we used a case definition that required only an HZ diagnosis code from inpatient or physician office visit claims and not antiviral drug use. In this sensitivity analysis, the exclusion for prior antiviral use was not applied so as to be methodologically consistent.

Other Safety Outcomes of Interest

In addition to HZ, the occurrence of several groups of prespecified safety outcomes within 42 days after vaccination were examined, including varicella/chickenpox (*ICD-9-CM* code 052.X) and non–HZ-specific hospitalization for meningitis and encephalitis (*ICD-9-CM* codes 047.8, 047.9, 049.9, 321.2, 321.8, 322.0-322.2, and 322.9) (conditions that could represent complications of disseminated varicella).

Statistical Analysis

We examined the distribution of vaccinated and unvaccinated person-time accrued during follow-up by patient characteristics. We then calculated HZ incidence rates by dividing the number of HZ cases by the number of corresponding person-years in subgroups of person-time stratified by vaccination status (unvaccinated, ≤42 days following vaccination, and >42 days following vaccination) and by exposure to medications of interest. The objectives of the stratified analysis were to evaluate HZ incidence rates during vaccinated person-time by comparing them with incidence rates during unvaccinated person-time and to control for confounding by biologics and immunosuppressive medication use. The methods developed by Hanley and Lippman-Hand[17] was used to estimate the 95% CI for rates where no cases were observed.

Proportional hazard regression models with age as the time axis were used to assess the association between zoster vaccine and HZ adjusting for sex, race, immune-mediated disease, time-varying concurrent medications, and time-varying health care utilization (hospitalization and physician visits). The proportional hazard assumption was tested by including a time × vaccine interaction term in the regression model. A 2-sided $P < .05$ was considered statistically significant. All analyses were performed using SAS version 9.2 (SAS Institute).

The institutional review board at the University of Alabama at Birmingham approved the study protocol and waived the requirement for informed consent. Use of the Medicare data was governed by a data use agreement (DUA) with the Centers for Medicare & Medicaid Services. As required by the DUA, any nonzero data cell containing fewer than 11 beneficiaries was not shown.

Table 1. Distribution of Person-Years of Follow-up by Herpes Zoster Vaccination Status and Patient Characteristics Among Medicare Beneficiaries

Patient Characteristics	Person-Years, No.	Vaccination Status, %	
		Vaccinated (10 868 Person-Years)	Unvaccinated (854 609 Person-Years)
Age, y			
60-69	292 723	27.7	33.9
70-79	371 315	51.0	42.8
≥80	201 439	21.3	23.3
Sex			
Women	637 704	72.3	73.7
Men	227 773	27.7	26.3
Race			
Black	65 102	1.4	7.6
White	749 442	93.9	86.5
Other	50 933	4.7	5.9
Type of immune-mediated disease			
Rheumatoid arthritis	557 751	52.2	64.6
Psoriatic arthritis	21 680	2.9	2.5
Psoriasis	161 816	26.3	18.6
Inflammatory bowel diseases	117 263	17.4	13.5
Ankylosing spondylitis	6967	1.2	0.8

RESULTS

A total of 463 541 patients were included in the analysis, including 4026 diagnosed with ankylosing spondylitis, 66 751 with inflammatory bowel disease, 11 030 with psoriatic arthritis, 89 565 with psoriasis, and 292 169 with RA. The mean (SD) age at the start of follow-up was 74 (8) years, the median duration of follow-up was 2.0 years (interquartile range, 0.8-3.0), 72.3% were women, and 86.3% were white. During the study, 18 683 patients (4.0%) received the zoster vaccine. The actual day of vaccination was available for 7780 patients. Most of the vaccinations (>70%) were performed by internal medicine and family practice physicians. TABLE 1 presents the distribution of person-years by vaccination status and other patient characteristics. Women, white patients, and RA patients contributed more vaccinated person-time than men, patients of other races, and patients diagnosed

Table 2. Herpes Zoster Incidence Rate While Unvaccinated by Medication Exposure

	Without Oral Glucocorticoids		With Oral Glucocorticoids		
Medications, Mutually Exclusive Groups[a]	HZ Cases, No.	HZ IR (95% CI)	HZ Cases, No.	HZ IR (95% CI)	IR Ratio (95% CI)
Any anti-TNF[b]	741	12.6 (11.8-13.6)	627	23.0 (21.3-24.9)	1.8 (1.6-2.0)
Adalimumab	100	12.1 (9.9-14.7)	96	21.7 (17.7-26.5)	1.8 (1.4-2.4)
Etanercept	151	11.5 (9.8-13.5)	122	21.5 (18.0-25.6)	1.9 (1.5-2.4)
Infliximab	490	13.2 (12.1-14.4)	406	23.8 (21.6-26.2)	1.8 (1.6-2.1)
Other anti-TNFs	<11	15.5 (7.8-31.1)	<11	31.3 (14.1-69.6)	2.0 (0.7-5.8)
Any non-TNF biologics[b]	107	14.0 (11.6-16.9)	119	18.7 (15.6-22.3)	1.3 (1.0-1.7)
Abatacept	53	12.1 (9.2-15.8)	62	17.1 (13.3-22.0)	1.4 (1.0-2.0)
Rituximab	46	17.1 (12.6-22.4)	52	20.2 (15.4-26.5)	1.2 (0.8-1.8)
Nonbiologic DMARDs without biologics	1184	10.8 (10.2-11.4)	1179	18.6 (17.6-19.7)	1.7 (1.6-1.8)
Methotrexate[c]	744	10.2 (9.5-10.9)	766	18.3 (17.0-19.6)	1.8 (1.6-2.0)
All other non–methotrexate DMARDs[d]	440	11.9 (10.8-13.1)	413	19.2 (17.5-21.2)	1.6 (1.4-1.8)

Abbreviations: DMARDs, disease-modifying antirheumatic drugs; HZ, herpes zoster; IR, incidence rate per 1000 person-years; IR ratio, crude incidence rate ratio comparing glucocorticoid-exposed to unexposed in each medication group; TNF, tumor necrosis factor.
[a] Classified using the following hierarchy: anti-TNF biologics with or without nonbiologic DMARDs; non-TNF biologics with or without nonbiologic DMARDs; nonbiologic DMARDs without biologics.
[b] Regardless of use of nonbiologic DMARDs.
[c] Regardless of use of other nonbiologic DMARDs.
[d] Alone or in combination.

with one of the 4 immune-mediated diseases other than RA.

HZ Incidence Rate While Unvaccinated

Among unvaccinated persons, the HZ incidence rate differed by exposure to medications commonly used in these patient populations (TABLE 2). Exposure to oral glucocorticoids was associated with a 1.2- to 2.0-fold greater risk of HZ; the increase was significant for most medication groups.

HZ Incidence Rate Within 42 Days

A total of 7780 vaccinated patients contributed person-time within 42 days after vaccination; fewer than 11 HZ cases were observed, resulting in an overall incidence rate of 7.8 cases per 1000 person-years (95% CI, 3.7-16.5). Among 633 patients exposed to biologics, including 551 patients exposed to anti-TNF biologics, no cases of varicella or HZ occurred within the 42 days following vaccination (95% CI, 0-5.4 cases per 1000 anti-TNF users and 0-4.7 per 1000 biologic users). Among all patients, we identified only 1 case of primary varicella (*ICD-9-CM* code 052.X) within the 42-day risk window, occurring on day 10 after vaccination. This patient was not exposed to any biologics, nonbiologic DMARDs, or oral glucocorticoids during the 6 months before or after vaccination. We identified no case of hospitalized meningitis or encephalitis in the 42 days after vaccination.

HZ Incidence Rate After 42 Days

During the period of more than 42 days after vaccination, we observed 138 HZ cases during 20 639 person-years (6.7 cases per 1000 person-years; 95% CI, 5.7-7.9) (TABLE 3), resulting in a rate ratio of 0.58 when compared with the incidence rate during unvaccinated person time (11.6 cases per 1000 person-years; 95% CI, 11.4-11.9; $P < .001$). Lower rates were observed during vaccinated person-time compared with unvaccinated person time in all subgroups of patients categorized by medication exposure.

After controlling for demographics, type of immune-mediated disease, health care utilization, and exposure to biologic and nonbiologic DMARDs and oral glucocorticoids, the adjusted hazard ratio of HZ associated with vaccination was 0.61 (95% CI, 0.52-0.71) (TABLE 4). The proportional hazard assumption was not violated.

Sensitivity Analysis

Results supporting the safety and efficacy of vaccination were consistent regardless of which outcome definition was used. When the more sensitive case definition requiring only an HZ diagnosis code was applied, no cases of HZ or varicella were observed during the 42 days following vaccination in the group exposed to anti-TNF or other biologics. The adjusted hazard ratio for vaccination was 0.67 (95% CI, 0.59-0.75) using this more sensitive definition (Table 4). When patients with unknown vaccine administration dates were censored at time of vaccine purchase, the results were again consistent (adjusted hazard ratio, 0.69; 95% CI, 0.56-0.86).

COMMENT

Our study examined the association between the receipt of zoster vaccine and HZ incidence in the short-term and over a median of 2 years of follow-up in a population of individuals with selected immune-mediated diseases. Patients with these diseases were excluded from previous vaccine trials and observational studies[4,18] because their commonly used treatments presented a contraindication to the live zoster vaccine. Our results were based on 18 683 vaccinated patients, including 633 who were exposed to anti-TNF or other biologics at the time of or within 42 days after vaccination; none of 633 patients

had evidence of varicella or HZ, suggesting that the zoster vaccine given in the setting of current biologic use may not be associated with a short-term increase in the risk for varicella or HZ. Moreover, the adjusted hazard ratio for the vaccine was 0.61, suggesting that vaccination was associated with decreased HZ risk over a median of 2 years of follow-up.

We did not identify any safety signal in the use of biologic therapies within 42 days after vaccination, a result that is consistent with our smaller, prior study using data from 44 115

Table 3. Herpes Zoster Incidence Rate for Unvaccinated and After Vaccination[a]

	>42 Days Since Vaccination		Unvaccinated	
	HZ Cases, No.	HZ IR	HZ Cases, No.	HZ IR
Overall	138	6.7 (5.7-7.9)	9960	11.6 (11.4-11.9)
Medications, mutually exclusive groups[b]				
Biologics, regardless of concomitant DMARDs or oral glucocorticoids	14	8.5 (5.1-14.4)	1592	16.0 (15.2-16.8)
Anti-TNF therapies	12	8.5 (4.8-15.0)	1368	15.9 (15.1-16.8)
DMARDs, without biologics but regardless of oral glucocorticoids	25	7.0 (4.7-10.3)	2363	13.6 (13.1-14.2)
Oral glucocorticoids alone	21	10.3 (6.7-15.8)	2080	17.2 (16.5-17.9)

Abbreviation: DMARDs, disease-modifying antirheumatic drugs; HZ, herpes zoster; IR, incidence rate per 1,000 person-years; TNF, tumor necrosis factor.
[a] More than 42 days after vaccination.
[b] Classified using the following hierarchy: biologics with or without nonbiologic DMARDs or oral glucocorticoids; nonbiologic DMARDs with or without oral glucocorticoids; oral glucocorticoids only.

Table 4. Adjusted Hazard Ratios for Herpes Zoster Incidence

	Definition of HZ Case			
	ICD-9-CM Diagnosis Code + Pharmacy Claim[a]		*ICD-9-CM* Diagnosis Code Only	
Patient Characteristics	No. of Cases/ Person-Years	HR (95% CI)	No. of Cases/ Person-Years	HR (95% CI)
HZ vaccination				
No	9960/855 226	1 [Reference]	16 486/860 907	1 [Reference]
Yes	145/21 436	0.61 (0.52-0.71)	259/21 674	0.67 (0.59-0.75)
Sex				
Men	2245/231 092	1 [Reference]	3707/232 243	1 [Reference]
Women	7860/645 570	1.22 (1.17-1.28)	13 038/650 338	1.21 (1.17-1.26)
Race				
White	9010/759 611	1 [Reference]	14 913/764 835	1 [Reference]
Black	546/65 427	0.67 (0.62-0.73)	928/65 798	0.69 (0.64-0.74)
Other	549/51 624	0.89 (0.81-0.97)	904/51 948	0.89 (0.83-0.95)
Immune-mediated disease				
Rheumatoid arthritis	7026/564 205	1 [Reference]	11 627/567 975	1 [Reference]
Ankylosing spondylitis	73/7173	0.98 (0.77-1.25)	114/7263	0.94 (0.77-1.13)
Inflammatory bowel diseases	1266/118 990	1.03 (0.97-1.10)	2129/119 707	1.02 (0.97-1.07)
Psoriatic arthritis	228/21 993	0.92 (0.80-1.05)	370/22 232	0.92 (0.83-1.02)
Psoriasis	1512/164 302	0.99 (0.93-1.05)	2505/165 405	0.97 (0.93-1.02)
Hospitalized in the previous 6 mo				
No	7858/711 601	1 [Reference]	12 323/716 662	1 [Reference]
Yes	2247/165 061	1.00 (0.95-1.05)	4422/165 920	1.25 (1.20-1.29)
No. of physician visits in the previous 6 mo[b]		1.04 (1.04-1.04)		1.04 (1.04-1.04)
DMARDs, exclusive groups[c]				
Nonbiologic DMARDs	2390/177 209	1 [Reference]	3892/180 078	1 [Reference]
Anti-TNF biologics	1380/87 374	1.15 (1.08-1.23)	2103/89 195	1.10 (1.04-1.16)
Non-TNF biologics	226/14 057	0.99 (0.86-1.13)	388/14 420	1.05 (0.94-1.16)
None	6109/698 021	0.84 (0.80-0.88)	10 358/598 890	0.86 (0.82-0.89)
Oral glucocorticoid use				
No	6060/655 033	1 [Reference]	10 122/657 219	1 [Reference]
Yes	4045/221 629	1.79 (1.71-1.86)	6623/225 362	1.69 (1.64-1.75)

Abbreviations: DMARDs, disease-modifying antirheumatic drugs; HR, hazard ratio; HZ, herpes zoster; *ICD-9-CM*, *International Classification of Diseases, Ninth Revision, Clinical Modification*; TNF, tumor necrosis factor.
[a] For acyclovir, famciclovir, or valacyclovir within 7 days of HZ diagnosis.
[b] Incremental effect associated with each additional physician visit.
[c] Classified using the following hierarchy: anti-TNF biologics with or without nonbiologic DMARDs; non-TNF biologics with or without nonbiologic DMARDs; nonbiologic DMARDs without biologics.

younger patients enrolled in a private commercial US health plan with these same 5 diseases.[19] In that study, far fewer patients were vaccinated (n=551) and only 47 were exposed to biologics within 30 days of vaccination. Although none of the 47 patients developed HZ within 42 days after vaccination, the number of patients in that study was too few to provide meaningful estimates of vaccine safety. In a case series of 17 patients revaccinated with the live yellow fever vaccine in Brazil while being treated with infliximab, none reported any occurrence of vaccination-related viscerotropic disease.[20] Although it might be argued that this study is not relevant because it examined the administration of a booster vaccine and not primary vaccination, the live zoster vaccine also represents a booster in as much as 99.6% of adults older than 40 years in the United States have a history of primary varicella infection.[21] In addition, the live varicella vaccine has been shown to be safe and protective against primary varicella infection and HZ in HIV-infected children.[22,23]

Although we did not identify any cases of varicella or HZ within the first 42 days after vaccination among those exposed to biologics, the observation of the zero numerator should not be interpreted to suggest that there is no risk. Instead, the upper bound of its 95% CI suggests that the cumulative incidence of varicella or HZ within 42 days in these patients could be as high as 4.7 cases per 1000 patients. Despite the use of 100% data from Medicare beneficiaries with fee-for-service coverage diagnosed with these diseases, we identified only 633 subjects exposed to anti-TNF or other biologics within 42 days after vaccination and some of our 95% CIs were wide. However, the 100% Medicare data likely represent one of the largest resources available to study safety outcomes in older patients with immune-mediated diseases.

Another limitation relevant to the safety results was that for HZ cases occurring shortly after vaccination, we were unable to determine whether the HZ cases were caused by the vaccine virus strain or the wild-type virus strain, which is possible if biological samples from skin lesions were available for analysis.[4] Additionally, given that our patients consisted of a disease-based cohort, it is theoretically possible that the 42-day risk window used for safety may be too short to capture all relevant safety events; however, use of a longer window has the potential to dilute safety data and mask safety signals.

Our study has several additional limitations. The occurrence of the outcome, HZ, was ascertained through examining administrative claims from physicians or hospitalizations and not confirmed with medical records review. To address this limitation, we used 2 different case definitions that are complementary with regard to their diagnostic properties. In the validation study of an algorithm that used only an HZ diagnosis code, 2 major reasons for misclassification were use of HZ codes for history of HZ (ie, prevalent disease) or for categorizing signs and symptoms as part of a differential diagnosis.[16] In light of this finding and to improve on the PPV that was estimated to be between 85% and 100%,[15,16] we required our primary case definition to have both HZ diagnosis codes and pharmacy claims for antiviral use. Regardless of the case definition used, the results were consistent.

Misclassification of medication exposure may have also occurred if patients were told to discontinue temporarily their medications before and after vaccination and yet still refilled their prescriptions. However, this would not apply to a majority of our patients who received infused biologics such as infliximab. Another limitation of the study was that we did not have and could not control for clinical (ie, disease severity) or other factors. If zoster vaccine was selectively given to healthier patients, we may have overestimated the protective effect of the vaccine.[19] Yet another limitation was that the actual vaccine administration dates were unknown for 59% of our patients, which resulted in the exclusion of these patients from safety (but not the effectiveness) analyses.

In conclusion, our data suggest that the live zoster vaccine may not be associated with increased risk of HZ shortly after vaccination in patients currently treated with biologics and that it is possibly associated with a significantly reduced longer-term HZ risk in patients with immune-mediated disease. Despite the recognition that patients with immune-mediated conditions are at increased risk of HZ, this and previous studies have shown that only a small fraction of these patients received the vaccine, likely in part due to safety concerns. Our data call into question the current recommendations that HZ vaccine is contraindicated in patients receiving biologics and suggest a need for a randomized controlled trial to specifically address the safety and effectiveness of HZ vaccination among patients receiving biologics.

Author Contributions: Dr Curtis had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Zhang, Delzell, Chen, Curtis.
Acquisition of data: Curtis.
Analysis and interpretation of data: Zhang, Xie, Delzell, Chen, Winthrop, Lewis, Saag, Baddley, Curtis.
Drafting of the manuscript: Zhang, Delzell, Winthrop, Curtis.
Critical revision of the manuscript for important intellectual content: Zhang, Xie, Delzell, Chen, Lewis, Saag, Baddley, Curtis.
Statistical analysis: Zhang, Xie, Delzell, Chen, Winthrop, Curtis.
Obtained funding: Curtis.
Administrative, technical, or material support: Zhang, Winthrop, Baddley, Curtis.
Study supervision: Saag, Curtis.
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