Severe Autoimmune Adverse Events Post Herpes Zoster Vaccine: A Case-Control Study of Adverse Events in a National Database

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ABSTRACT

Zoster vaccine is recommended to reduce the incidence of herpes zoster and its complication of postherpetic neuralgia in older adults. However, there have been reports of autoimmune side effects post vaccination. We therefore aim to investigate the possible relationship of severe autoimmune adverse events (arthritis, vasculitis, systemic lupus erythematosus, thrombocytopenia, alopecia, Guillain-Barre syndrome, optic neuritis and multiple sclerosis) post zoster vaccination with a matched case-control study of reported events in the Vaccine Adverse Event Reporting System (VAERS). Our study showed no significantly increased risks of severe autoimmune adverse events, except arthritis and alopecia, after vaccination. Compared to the unexposed, patients with zoster vaccination had 2.2 and 2.7 times the odds of developing arthritis and alopecia, respectively ($P<0.001$ and $P=0.015$, respectively). However, almost none of these events was life threatening. Zoster vaccine is, therefore, relatively safe and unlikely to exacerbate or induce autoimmune diseases. Given its benefits and safety but low coverage, dermatologists and primary care physicians should encourage zoster vaccine use in elderly patients, including selected patients with autoimmune diseases.

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INTRODUCTION

Zoster vaccine (Zostavax®) is a live attenuated vaccine recommended for healthy adults 60 years or older to reduce the incidence of herpes zoster.[1] Patients with autoimmune diseases, such as rheumatoid arthritis (RA), are found to have a 1.5 to 2 fold increased risk for herpes zoster, compared to the general population.[2] As a result, in 2012, the American College of Rheumatology (ACR) recommended zoster vaccine for older RA patients receiving non-biologic disease-modifying antirheumatic drugs (DMARD) therapies or before starting DMARD or biologic treatment.[2] However, cases of autoimmune adverse effects such as arthritis, vasculitis, systemic lupus erythematosus (SLE), thrombocytopenia, alopecia, Guillain-Barre syndrome (GBS), optic neuritis, and multiple sclerosis after zoster vaccinations have been reported in the Vaccine Adverse Event Reporting System (VAERS), a national vaccine monitoring system in the United States. There have also been published case reports of bullous pemphigoid following vaccination.[3,4]

Hepatitis B virus (HBV) and Human Papillomavirus (HPV) vaccines have also been reported to be associated with an increased risk of serious autoimmune adverse events (SAAEs). There were several published case reports of SAAEs following HBV[5,6] and HPV[7,8] vaccination. Case series and case-control studies had also demonstrated increased risks of SAAEs post HBV and HPV vaccinations,[9-12] though there were other studies that showed conflicting results.[13-15] Therefore, it is important to evaluate whether zoster vaccine also results in an increased risk of autoimmunity. In this study of adverse events reported in the VAERS monitoring database, we aim to investigate if zoster vaccination is associated with an increased risk of autoimmune adverse effects using a previously established matched case-control study methodology.[16]

METHODS

The VAERS is a national vaccine safety surveillance database maintained jointly by the U.S. Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) to analyze adverse events following immunization. They periodically followed up on specific serious adverse events and deaths recorded in the VAERS.

The VAERS was analyzed using a matched case-control study design previously described by Geier et al.[16] in 2005. Information regarding SAAEs following zoster vaccination was retrieved from the VAERS database using the CDC Wonder online interface (http://wonder.cdc.gov/vaers.html). Since the zoster vaccine was approved and licensed by the FDA in May 2006, all SAAEs associated with vaccines administered from May 2006 through November 2014 were identified as cases. The SAAEs were specified as arthritis (VAERS codes: 10003246 or 10039073), vasculitis (VAERS code: 10047115), SLE (VAERS code: 10042945), thrombocytopenia (VAERS code: 10050245, 10021245, 10043554, or 10043561), alopecia (VAERS code: 10001760 or 10073736), GBS (VAERS code: 10018767), as well as optic neuritis and multiple sclerosis (VAERS code: 10030942 and 10028245). Patients who received zoster vaccine were considered exposed, while those

TABLE 1.

Summary of Serious Autoimmune Adverse Events (SAAEs) After Zoster Vaccine

SAAEs (n)	Life threatening	Permanent disability	Median onset of symptoms in days
Alopecia (13)	0	0	4
Arthritis (42)	1	5	4
GBS* (25)	8	4	15-30
MS* + ON* (5)	0	2	0
SLE* (4)	1	1	7
Thrombocytopenia (9)	5	0	8
Vasculitis (4)	1	0	3

*GBS: Guillain-Barre Syndrome; MS: Multiple Sclerosis; ON:Optic Neuritis; SLE: Systemic Lupus Erythematosus.

who did not receive any zoster vaccine but received tetanus toxoid-containing vaccines in the VAERS database within the same time frame were considered unexposed. Tetanus toxoid-containing vaccines are not known to be associated with SAAEs.[16] The cases and controls were then matched based onage and gender, with each case having at least one matched control.

The controls were selected from patients with a set of outcomes that had previously been shown to be neither associated with the exposed nor the unexposed groups.[16] These were identified to account for potential confounders or systemic errors in the VAERS database. These control outcomes include cardiovascular disorder (VAERS code: 10007649), cerebrovascular accident (VAERS code: 10008190), medication error (VAERS code: 10027091), urinary tract infection (VAERS code: 10046571), and death (VAERS code: 10011906).

The statistical package for social sciences (IBM SPSS Verson 22) was utilized to perform the Fisher's exact test and evaluate statistical significance. Odds ratio (OR), 95% OR confidence interval (CI), and *P*-values were calculated to test the null hypothesis that zoster vaccine was not associated with SAAEs. A two-sided *P*-value of < 0.05 was considered statistically significant.

RESULTS

A total of 18534 adverse events were reported after zoster vaccination from May 2006 to November 2014 in the VAERS database. Out of these, 102 events were SAAEs. More than half (64.7%) of these events occurred in females. The median age of patients who developed SAAEs was above 65 years old. The median time of onset to each event is about seven days. Table 1 shows a summary of the SAAEs reported for zoster vaccine. Arthritis has the highest number of reported adverse events (n = 42), followed by GBS (n = 25). More than half of the thrombocytopenia cases (n = 5) were deemed to be life threatening, while approximately a third of the GBS cases (n = 8) were considered life threatening.

Table 2 shows the ORs for various SAAEs. There was a significant increase in the odds of alopecia and arthritis in patients who received the zoster vaccine, compared to those who received the tetanus toxoid-containing vaccine. Patients who received zoster vaccine had 2.7 times the odds of having arthritis (95% CI: 1.7 to 4.3, $P<0.001$) and 2.2 times the odds of developing alopecia (95% CI: 1.2 to 4.3, $P= 0.015$). For other autoimmune adverse events, including GBS, multiple sclerosis, optic neuritis, SLE, thrombocytopenia, and vasculitis, there were no significantly increased odds among those who received the zoster vaccine, compared to those who received the tetanus toxoid-containing vaccine.

DISCUSSION

Herpes zoster is more common and severe in older adults and patients with immunosuppression.[1] The condition can potentially be serious and persistently painful, which substantially reduces daily functioning and quality of life of affected patients.[1] It has been demonstrated that the vaccine decreases the likelihood of developing herpes zoster and postherpetic neuralgia by 51% and 67%, respectively.[17] Patients with certain autoimmune diseases are frequently mildly immunosuppressed.[2] Zoster vaccine would be useful in such patients to prevent herpes zoster reactivation as well as its sequela.

> "Being a live attenuated vaccine, there have been concerns about its use in patients with autoimmune diseases, who may be immunosuppressed to a certain degree."

Zoster vaccine contains residual components of MRC-5 cells, including DNA and protein, as well as bovine calf serum,[18] which can theoretically induce autoimmunity. As a DNA vaccine, it may contain antigens that cross-react with self antigens, causing

TABLE 2.

Summary of Odds Ratio for Serious Autoimmune Adverse Events Post Zoster Vaccine

Type of adverse events	Number of cases	Number of controls	Odds ratio (95% CI)	p value
Alopecia				
Exposed	13	40	2.2 (1.2 – 4.3)	0.015
Unexposed	88	606		
Arthritis				
Exposed	42	61	2.7 (1.7 – 4.3)	< 0.001
Unexposed	98	387		
GBS*				
Exposed	25	174	0.73 (0.46 – 1.2)	0.18
Unexposed	104	527		
Multiple Sclerosis & Optic Neuritis				
Exposed	5	30	0.62 (0.23 – 1.7)	0.34
Unexposed	47	174		
SLE*				
Exposed	4	10	0.74 (0.23 – 2.4)	0.62
Unexposed	76	141		
Thrombocytopenia				
Exposed	9	46	1.4 (0.65 – 0.9)	0.40
Unexposed	84	591		
Vasculitis				
Exposed	4	16	0.94 (0.31 – 2.9)	0.91
Unexposed	83	311		

*GBS: Guillain-Barre Syndrome; SLE: Systemic Lupus Erythematosus.

activation of autoreactive B cells to secrete IgG anti-DNA autoantibodies.[19,20] The adjuvants in the vaccine can also stimulate the production of polyclonal autoantibodies.[21] These processes can either induce or exacerbate autoimmune diseases.

In this study, we found no significant relationship between most autoimmune adverse events and zoster vaccine. The odds of developing vasculitis, thrombocytopenia, GBS, demyelinating neurological conditions, and SLE were not significantly increased post immunization. However, we noticed increased odds of developing arthritis and alopecia after zoster vaccine, compared to age- and gender-matched controls, suggesting a possible association. The presentation of arthritis might have been secondary to serum sickness reaction to recent zoster vaccine, which contains bovine calf serum.[22] Some cases of arthritis were assessed and diagnosed by rheumatologists. Physical examination and laboratory data, however, were either not available or incomplete for some cases of arthritis and alopecia. There have also been no published case reports in the scientific literature regarding the development of arthritis or alopecia after zoster vaccine. This association might be more formally evaluated by a long-term cohort study of patients immunized with zoster vaccine.

Being a live attenuated vaccine, there have been concerns about its use in patients with autoimmune diseases, who may be immunosuppressed to a certain degree. However, recent studies have shown that zoster vaccine is relatively safe in such patients.[23,24] Despite its benefits and safety, there is still low coverage of the vaccine. The CDC had previously reported that only 20.1% of elderly patients 60 years or older received herpes zoster vaccine in 2012.[25] Overall, Caucasians aged 60 years or older had the highest vaccination rate (22.8%), followed by Asians (16.9%), African Americans (8.8%), and, lastly, Hispanics (8.7%).[25] Possible barriers to widespread coverage include high financial costs as well as lack of patients' awareness and physician's recommendation.[26]

Our study utilized a case-control study method previously reported in the literature[16] to evaluate cases in the VAERS database. Events with the abovementioned defined SAAEs form the cases in our study. They were matched in terms of age and gender to controls. For each autoimmune adverse event, we evaluated the exposure (zoster vaccine versus tetanus toxoid-containing vaccine) among all cases and controls to account for autoimmune side effects secondary to other vaccines, such as HBV and HPV vaccines. The VAERS Working Group of the CDC had previously stated that self-reported adverse events by patients accounted for less than 5% of the total cases.[27] Most cases were confirmed by physician assessment. Information from the VAERS database is readily available and updated regularly in a timely fashion. However, the database has the potential

limitations of confounding factors and systemic errors from under-reporting, erroneous reporting, multiple exposures, or multiple outcomes.[27] In our study, we have taken care to match the cases to controls to account for possible confounding by age and gender. We have also evaluated all the cases for double reporting. However, there might still be unknown confounders and some adverse events may be coincidental. It is important to note that, even though the VAERs database may be used to document any possible associations, it does not establish any cause and effect relationship between vaccines and adverse events. In conclusion, the present study demonstrated that zoster vaccination carries no increased risks of severe autoimmune adverse events. Although there were reports of SAAEs after zoster vaccination in the VAERS database, they did not occur more frequently than other vaccines. Therefore, dermatologists and primary care physicians should encourage more zoster vaccine use in elderly patients, including selected patients with autoimmune diseases. More follow-up studies or assessment of other vaccine safety databases should be performed to better evaluate the association.

DISCLOSURES

The authors declare that they have no conflicts of interest.

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