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Apparent lack of association of COVID-19 vaccination with Herpes Zoster

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ABSTRACT

Purpose: Herpes zoster (HZ) has been identified as a potential association with the BNT162b2 COVID-19 vaccination. This study evaluated this possible association in a cohort of patients receiving the vaccination.
Methods: Epic electronic health records of adult patients who received at least one COVID-19 vaccination between January 12, 2020 and 9/30/2021 within the NYU Langone Health were reviewed to analyze a new diagnosis of herpes zoster within 3 months before compared to 3 months after vaccination.
Results: Of the 596,111 patients who received at least one COVID-19 vaccination, 716 patients were diagnosed with HZ within three months prior to vaccination, compared to 781 patients diagnosed within 3 months afterwards. Using the chi-square test for independence of proportions, there was not a statistically significant difference in frequency of HZ before (proportion: 0.0012, 95% CI: [0.0011, 0.0013]) vs. after vaccination (proportion: 0.0013, 95% CI: [0.0012, 0.0014]); ($p = 0.093$).
Conclusions and importance: This study did not find evidence of an association between COVID-19 vaccination and a new diagnosis of HZ. We encourage health care professionals to strongly recommend COVID-19 vaccinations per Centers for Disease Control (CDC) recommendations and vaccination against HZ according to Food and Drug Administration (FDA) approval for the recombinant zoster vaccine.

1. Introduction

Herpes Zoster (HZ), also known as shingles, is caused by local reactivation of the varicella zoster virus (VZV). Following chicken pox, the primary infection, VZV remains latent in sensory ganglia and may reactivate when cell mediated immunity declines due to age, immunosuppression or unknown reasons[1].

Herpes zoster has been identified as potentially associated with the BNT162b2 COVID-19 vaccine at 15.8 events per 100,000 persons (95% CI, 8.2 to 24.2) as well as in a number of clinical case reports.[1–8] Skepticism about the safety of the COVID-19 vaccine is the most commonly cited reason for vaccine hesitancy and continues to present a major obstacle to achieving broad vaccination coverage.[9] We conducted a pilot study exploring the potential relation between COVID-19 vaccines and HZ at a large urban academic health center.

2. Materials and methods

Using Epic electronic medical records, we identified patients 18 years of age and older who were vaccinated against COVID-19 at NYU Langone Health (NYULH) between January 12, 2020 and 9/30/2021 and had been patients during the preceding 18 months. Written consent to publish this case has not been obtained as this report does not contain any personal identifying information. Herpes zoster was identified through international classification of diseases (ICD-10) codes utilized in the Epic electronic medical record under B02 (herpes zoster) and all sub-codes including: B02.9 (zoster without complications), B02.7 (disseminated zoster), B02.39 (other zoster eye disease), and others. No information was collected on if patients were evaluated at outside medical systems, as it was thought that patients who were seen at NYULH in the preceding 18 months would stay in the system for their care. We evaluated the frequency of a new diagnosis of HZ within 3 months prior to COVID-19 vaccination compared to 3 months

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afterwards with chi square test for independence of proportions.

3. Results

Of 596,119 vaccinated patients, 716 patients were diagnosed with HZ within three months prior to vaccination (proportion: 0.0012, 95% CI: [0.0011, 0.0013]), compared to 781 patients diagnosed within 3 months afterwards (0.0013, 95% CI: [0.0012, 0.0014]). Using the chi-square test for independence of proportions, there was not a statistically significant difference in infection incidence before and after vaccination ($\chi^2 = 2.826$, $p = 0.093$).

4. Discussion

Since the emergency use authorization of COVID-19 vaccinations and the launch of mass vaccination campaigns, over 7000 cases of herpes zoster were reported through the Vaccine Adverse Event reporting system in the United States.[10] However, a definitive association of the COVID-19 vaccinations and herpes zoster remains uncertain. In our cross-sectional study, we have not found an increase in the frequency of HZ following vaccination against COVID-19. Our analysis included patients who received any of the three available COVID-19 vaccines at NYULH, including 2 mRNA and one adenovirus vector, and was not specific to the BNT162b2 vaccine.

The consensus amongst the scientific community is that COVID-19 vaccines are safe and effective with mild side effects including mild to moderate pain at injection site, fatigue, and headache.[11,12] In individuals with underlying conditions that may impair immunity or those receiving immunomodulating therapy, observations indicate Covid 19 vaccination is efficacious and safe.[13] Nonetheless, concerns about the safety of vaccines produced over a short time span and the hesitancy about unforeseen side effects are barriers towards reaching vaccination goals.[14,15]

Epidemiological studies of COVID-19 vaccine are limited but recent evidence from Preta et al. demonstrated increased relative risk of HZ in the setting of mRNA COVID-19 vaccination (odds ratio 1.9, 95% CI [1.8–2.1]) compared to influenza vaccines in a cohort of 716,928 cases.[6] Several case reports have also identified herpes zoster shortly following the COVID-19 vaccine.[3–5,7,8] Some of these cases have been attributed to immunosuppression of the vaccine recipient, but cases have also been reported in immunocompetent patients.[16] In one patient, reactivation of VZV was thought to be linked to his underlying immune dysregulation secondary to AIDS.[17] However, causality between vaccination and zoster has yet to be elucidated. Chu et al. reviewed four cohort studies and demonstrated that there was no evidence that the COVID-19 vaccine was associated with an increased risk of herpes zoster (Risk ratio: 1.06, 95% CI 0.91 TO 1.24).[18]

COVID-19 vaccines have been shown to cause massive T-cell activation, particularly of $CD8^+$ T cells and $CD4^+$ t cells.[19] It is theorized that in the setting of SARS-CoV-2 vaccination, $CD8^+$ T cells shift to build immunity to the new antigens and are no longer able to keep VZV in the latent state.[20]

An important caveat to this discussion is that COVID-19 itself has been linked to herpes zoster infection. A leading hypothesis is that SARS -CoV-2 is associated with T cell immune dysfunction, particularly through lymphopenia and cytokine storm.[21] In one public health study in Brazil, the occurrence of HZ was noted to be increased by 35.4% at the height of the pandemic [25]. Further epidemiological investigation of the relationship of Covid-19 infection to HZ will be necessary.

There are several limitations of our study, and caution is needed in interpreting the results of this pilot study. Our study population included persons who had been seen at NYULH during the 18 months prior to vaccination making it likely they would return for care after COVID-19 vaccination, but does not include persons diagnosed with zoster elsewhere after vaccination. A sub-group analysis by type of COVID-19 vaccine is beyond the scope of this paper, but given the similar number of cases of zoster pre and post vaccination, would be unlikely to change the results. Although analysis by age and immune status of our COVID-19 vaccinated study population is beyond the scope of our paper, given that immunocompromised persons have been recommended to be vaccinated against COVID-19, and the median age of onset of zoster is 56 years, we think our study population includes persons at risk for zoster.[22]

Regarding our patient population, we examined rates of herpes zoster infection in all vaccinated individuals. This may lead to ascertainment bias since patients presenting for vaccination are more likely to interface with the healthcare system. We describe data from a large urban healthcare system located in an area with high vaccination rates. Future investigations should focus on diverse medical systems with different rates of vaccination.

While it is important to recognize possible side effects of vaccination against COVID-19, we believe the benefits far outweigh the risks. We encourage health care professionals to strongly recommend COVID-19 vaccination per Centers for Disease Control (CDC) recommendations and vaccination against HZ for persons aged 50 years and older and for immunocompromised persons aged 18 and older.[23,24]

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The following authors have no financial disclosures: S.P.,L.D.,S.G.,L. B.,E.C.

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