Herpes Zoster and Simplex reactivation following COVID-19 vaccination: new insights from a Vaccine Adverse Event Reporting System (VAERS) database analysis

Abstract

Background: A few cases of Herpes Zoster and Simplex reactivation following COVID-19 immunization have been recently described but the real extent of this suspect adverse event has not been elucidated yet.

Methods: We performed a nested case/control study by using the U.S. Vaccine Adverse Event Reporting System database. We carried out a case-level clinical review of all Herpes reactivation cases following the administration of COVID-19 vaccines. For cases and controls significance was set at P = 0.05, differential risk of reporting was assessed for each vaccine as reporting odds ratio and incidence was estimated based on the total number of vaccine doses administered.

Results: Of 6,195 cases included in the analysis (5,934 and 273 reporting Herpes Zoster and Herpes Simplex, respectively) over 90% were non-serious. We found a slightly higher risk of reporting both for Zoster (ROR = 1.49) and Simplex (ROR = 1.51) infections following the Pfizer-BioNTech vaccine. The estimated incidence was approximately 0.7/100,000 and 0.03/100,000 for Zoster and Simplex, respectively.

Conclusions: The paucity of cases (almost all of non-serious nature) makes the potential occurrence of this adverse effect negligible from clinical standpoints, thus supporting the good safety profile of the COVID-19 vaccination, which remains strongly recommended.

Keywords: COVID-19, herpes, pharmacovigilance, real-world evidence, vaccines.

1. Introduction

The family of Herpesviridae comprises nine DNA virus types extensively widespread among humans that typically cause cutaneous lesions (i.e., HHV-1, HHV-2, HHV-3) or more serious diseases, such as mononucleosis (HHV-4) and Kaposi's sarcoma (HHV-8). Specifically, at the first acute infections, HHV-1 and HHV-2 (Herpes Simplex viruses, HSV) rapidly replicate within dermal keratinocytes, leading to oral, perioral, skin and mucous lesions, including genital and ocular infections (e.g., herpetic keratitis) [1].

Conversely, HHV-3 (Varicella Zoster virus, VZV) manifests as a painful vesicular eruption along a dermatomal distribution, known as Herpes Zoster; its most frequent complication is post-herpetic neuralgia and in children (< 12 years old) it is the causative agent of chickenpox 2 [2–4]. After the primary infection, both HSV and VZV stay latent by persisting in sensory neurons (trigeminal or sacral ganglia for HSV; mainly dorsal root, enteric or trigeminal ganglia for VZV). The reactivation is mainly triggered by a secondary

immunodeficiency state, either age-related or iatrogenic (drugs, physical or emotional stress, tissue damage and exposure to UV light) factors, or due to concomitant diseases (e.g., HIV, cancer) [5–10].

Interestingly, several cases of Herpes reactivation have been recently described in patients affected by coronavirus disease 2019 (COVID-19). This newly emerged multisystemic disease is primarily characterized by respiratory-related symptoms, but may also involve other districts, including the nervous system. Furthermore, preliminary evidence has identified a range of potential dermatologic manifestations of COVID-19, such as diffuse erythematous rash and widespread or localized urticaria, as well as chickenpox-like vesicles, indicating a VZV reactivation, likely associated with the unbalanced immune status of the host [11–21]. In line with these findings, COVID-19 has been showing the ability to reactivate other viruses, including HHV-4, HHV-6, and HHV-7 [22]. Furthermore, some reports have speculated that the presence of an Herpes Zoster infection may be a sign for a recent subclinical COVID-19 diagnosis in younger age groups [15,19,20,23].

It is worth of mentioning that some of the above-mentioned cutaneous manifestations may also appear after immunization with vaccines expressing the SARS-CoV-2 spike (S) glycoprotein.

Currently, the U.S. Food and Drug Administration (FDA) amended the emergency use authorization for the following vaccines: BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), both lipid-nanoparticle encapsulated mRNA vaccines expressing the prefusion-stabilized S-protein, and Ad26.COV2.S (Janssen), a viral vector encoding the S-protein [24]. These state-of-the-art biotechnological tools have demonstrated more than 90% efficacy against symptomatic disease and severe outcomes for wild-type variants. As regards to the safety, the most commonly reported adverse events (AEs) following COVID vaccines are injection site pain, fever, headache, nausea, and vomiting, supporting an overall favorable safety profile [25–30]. Herpes reactivation has not been commonly associated with immunization; indeed, apart from VZV vaccination [31], only a few cases of Herpes Zoster following vaccination have been described to date: hepatitis A, rabies, and influenza have each been reported once [32], as well as a case of brachial plexus zoster after yellow fever vaccination [33] and an acute retinal necrosis, as complication of VZV infection after vaccination with the 2009 H1N1 influenza vaccine [34]. As for HSV, only two cases have been published in scientific literature so far, reporting an HSV-1 and an HSV-2 reactivation after influenza vaccination [35,36]. Accordingly, among the wide spectrum of cutaneous AEs induced by COVID-19 vaccines, neither HSV nor VZV reactivation are listed in the Summary of Product Characteristics (SPC) of any COVID-19 vaccine.

Evidence on this correlation is very limited; to date, approximately 60 cases of VZV reactivation following COVID-19 vaccination have been recently reported in the literature: symptoms emerged on otherwise healthy and immunocompetent patients and AEs resolved within a few days spontaneously or via oral antiviral therapy [37–57]. To date, three cases of COVID-19-induced HSV keratitis have been reported [58,59]. Moreover, an American registry-based study on 414 cutaneous AEs after Moderna vaccine administration retrieved 4 cases of HSV reactivation, along with 10 of VZV reactivation [60]. Similarly, a cross-sectional Spanish study of 405 cases reported 15 HSV and 41 VZV reactivations after COVID-19 vaccination [61].

Despite the well-known intrinsic limitations (such as under/over reporting), spontaneous reporting systems represent a valuable source to obtain real-world data on rare and unexpected AEs, to compare therapeutic options, to gain new insights on potential mechanisms of adverse drug reactions (ADR), thus contributing to better characterize the safety/effectiveness profile of drugs and vaccines used in the daily clinical practice [62,63].

We carried out a case/non-case analysis based on the Vaccine Adverse Event Reporting System-VAERS (a comprehensive database collecting all vaccine-related AE reports regarding vaccines approved by FDA), aimed at investigating the occurrence of Herpes reactivation following COVID-19 vaccination, estimating the risk for reporting our AE of interest according to the vaccine administered [64,65]. Since the public accessible version of the VAERS includes the case narrative, we were able to perform a case-level clinical review among a wide cohort of patients to further examine the correlation between Herpes reactivation and COVID-19 vaccinations. Most importantly, we were able to provide an estimate of the reporting rate of HSV and VZV reactivation based on the total number of vaccine doses administered in the USA.

2. Methods

2.1 Data source

VAERS is an early warning system co-managed by the Centers for Disease Control and Prevention (CDC) and the FDA and has a key role in detecting potential safety issues concerning FDA-approved vaccines. Since 1990, over 1,225,000 records have been filed by healthcare professionals and manufacturers, who are required to report any suspect AE that occur following vaccination, and also consumers. Each AE report is filed in the VAERS in the form of Individual Case Safety Report (ICSR), which provides the whole case narrative, accessible on the public version of the VAERS and comprehensive of administrative (e.g., Country and State of occurrence, qualification of the reporter) and demographic (e.g., patient sex, age, weight, previous AEs, chronic conditions) characteristics, AE (e.g., symptoms, seriousness, outcome, medical tests and laboratory results) and suspect vaccine (e.g., name, administration date, time to onset, route) details, along with information concerning any potential drug or vaccine administered at the time of AE but not held responsible for its occurrence by the reporter, referred to as “concomitant medication”. VAERS also performs a process of selection of higher quality cases, since it may request additional information from reporters and, whether multiple reports of a single AE are received, only the most updated version is included in the publicly accessible dataset.

While very important in monitoring vaccine safety, VAERS reports alone cannot be used to determine a causal relation between vaccine and event and should be interpreted in the context of other scientific information: since VAERS collects data on any AE occurring after vaccination, the report of an AE to VAERS does not prove that a vaccine truly caused the event described, but it just confirms that the reported event occurred after vaccine was given. Nevertheless, as part of CDC and FDA’s multi-system approach to post-marketing vaccine safety monitoring, VAERS is designed to rapidly detect potential unusual or unexpected patterns of AE reports,

also known as "safety signals", providing valuable information that must be further evaluated in order to assess a possible safety concern [66–70].

2.2. Data processing

All ICSRs submitted to the VAERS within the USA that reported at least one vaccine approved for COVID-19 immunization (Pfizer-BioNTech, Moderna, or Janssen) were retrieved (data updated to 12/03/2021).

Since completeness of data may vary from case to case through a process of systematic and manual cleaning, cases without information on patients age and sex, were detected and excluded, in order to select only higher quality data for our analysis. We then excluded all ICSRs describing an AE occurring after the exposure to more than one vaccine (either for COVID-19 immunization or other agents), as well as those that didn't specify which COVID-19 vaccine was administered (reported as "unknown COVID-19 vaccine" in the dataset).

2.3. Definition of cases and controls

In our nested case/control study, cases of interest were all ICSRs reporting one of the three COVID-19 vaccines and the occurrence of VZV or HSV infection. AEs are coded by using the Medical Dictionary for Regulatory Activities (MedDRA); all Preferred Term (PTs) used to identify cases of interest are listed in Supplementary Table 1. We excluded from our "cases" both non-specific Herpes infection cases and ICSRs that described a concomitant diagnosis of COVID-19 infection, since it also can lead to Herpes reactivation, as previously mentioned. ICSRs reporting COVID-19 infection were identified through the research of the following PTs in the "adverse event" section: "COVID-19", "SARS-CoV-2 test positive". We also excluded all ICSRs that explicitly reported an active Herpes infection at the time of administration in the section "case description".

Non-cases (controls) were all the remaining ICSRs included in our cohort, i.e., COVID-19 vaccine-induced AEs other than Herpes reactivation.

2.4. Descriptive analysis

Information on patient age and sex, AE onset interval, clinical outcome, PT used to identify Herpes reactivation, concomitant medication at time of AE onset, illness at time of vaccination, chronic conditions, prior vaccination AEs, prior COVID-19 infection, and allergies were searched for each case of interest and separately analyzed for HSV and VZV reactivation.

AE seriousness was not provided in our data source; however, in accordance with the International Council on Harmonization E2D guidelines an AE was defined as "serious" if it was fatal, threatened the life of the patient, required or prolonged hospitalization, resulted in persistent or significant disability/incapacity, determined a congenital anomaly/birth defect, or resulted in some other clinically important conditions [71]. Therefore, in order to estimate the seriousness of the AEs retrieved, we labeled each report as serious or non-serious based on these criteria.

The AE onset interval was calculated for all cases that reported both the date of administration and the date of AE onset.

Finally, to investigate the potential role of other drugs in causing or exacerbating Herpes reactivation, for each case we investigated the presence of immunosuppressive agents in the section "concomitant medication". We searched all drugs that exert their pharmacological action or their primary toxicity via immunosuppression. Among investigated immunosuppressants, we included also glucocorticoids, except when administered topically (all drugs included are listed in Supplementary Table 2).

In order to estimate the incidence of the AE of interest, we considered the most recent data provided by the CDC, from which we extracted the total number of doses administered in the USA up to 12/03/2021 [72].

2.5. Statistical analyses

Normality of data was checked for continuous variables and appropriate parametric and non-parametric analyses were performed for cases and non-cases, in terms of age, female sex, AE seriousness, exposure to concomitant medication and prior vaccination AEs. Student's t-test was used to assess whether age was distributed differently between cases and non-cases, whereas Pearson's $\chi 2$ test was used to assess whether categorical variables were differently distributed between cases and non-cases. Tests were 2-tailed, with significance set at a P value of 0.05.

In order to investigate the different reporting risk for VZV and HSV reactivation, we carried out a disproportionality analysis through the estimation of a Reporting Odds Ratio (ROR) and its 95% Confidence Interval (95% CI) for each COVID-19 vaccine. This statistical measure potentially allows the detection of an AE that is reported more frequently than expected using a 2x2 contingency table, which allows the estimation of the reporting rate of an AE of interest after the exposure to the tested drug or vaccine (A) compared to other AEs induced by the same agent (B) and to the same AE caused by other agents (C) and to all other reports in the cohort (D), by applying the following equation: ROR = (A/B)/(C/D) [73–75]. A signal of disproportionate reporting (SDR) arises when the lower bound of the ROR 95% CI is greater than the threshold value of 1 and general consensus agrees that at least three cases for each vaccine must be provided.

In order to estimate the incidence of the AE of interest, we divided the number of reports of the AE of interest by the number of doses administered in the USA up to 12/03/2021 and then multiplied it by 100,000.

The ROR for each vaccine/AE combination and the incidence were estimated for HSV and VZV reactivation separately.

Data tiding and statistical analyses were carried out using R (R Development Core Team, 2019).

3. Results

3.1. Study population

We identified 703,611 domestic ICSRs submitted to VAERS reporting at least one COVID-19 vaccine among suspected agents in the occurrence of an AE. Through our screening procedure, we selected 588,323 reports that fulfilled our inclusion criteria and represented our study cohort (Figure 1). Among these, we observed 6,195 cases of HSV or VZV reactivation following COVID-19 vaccination and without concomitant COVID-

19 diagnosis or concomitant active Herpes infection at time of AE onset, corresponding to 1.05% of all ICSRs of our cohort. Univariate analyses of demographics and characteristics of nested cases and non-cases populations are presented in Table 1.

3.1.1. VZV reactivation cases

We retrieved a total of 5,934 cases that reported VZV reactivation among AEs. Patients experiencing this AE had a mean age of 54 ± 16 years, which showed to be significantly higher than that of non-cases ($P < 0.001$), and a female prevalence of 69.67%, which instead did not significantly differ from non-cases ($P > 0.05$). A total of 4,137 (69.72%) patients suffered from chronic medical conditions, 78 (1.31%) patients had been previously infected by SARS-CoV-2 and 2,188 (36.87%) suffered from allergies to food, drugs or environmental allergens. Prior vaccination AEs were observed in 207 cases and were less frequently reported compared to non-cases (3.49% vs. 5.50%; $P < 0.001$): 6 of them reported shingles outbreak following the 2010 H1N1 vaccine (n = 1), a measles/mumps/rubella vaccine (n = 1), a diphtheria/tetanus/pertussis vaccine (n =1), an unspecified flu vaccine (n = 3), and the first dose of Moderna (n = 1) and Pfizer (n = 4).

VZV reactivation was described with the following PTs: “Herpes Zoster” (n = 5,819; 98.06%), “ophthalmic Herpes Zoster” (n = 60; 1.01%), “Herpes Zoster oticus” (n = 51; 0.86%), “Varicella Zoster virus infection” (n = 25; 0.42%), “Herpes Zoster reactivation” (n = 17; 0.29%), “disseminated Varicella Zoster virus infection” (n = 9; 0.15%), “Herpes Zoster meningitis” (n = 4, 0.07%), “Herpes Zoster cutaneous disseminated” (n = 3, 0.05%), “genital Herpes Zoster” (n =1; 0.02%), “Herpes Zoster infection neurological” (n = 1; 0.02%), and “Herpes Zoster meningoencephalitis” (n = 1; 0.02%). Overall, the most common PTs listed alongside VZV reactivation were: “rash” (n = 1,550; 26.12%), “pain” (n = 843; 14.21%), “headache” (n = 506; 8.53%), “pruritus” (n = 441; 7.43%), “blister” (n = 429; 7.23%), “fatigue” (n = 425; 7.16 %), “pain in extremity” (n = 368; 6.20%), “pyrexia” (n = 315; 5.31%), “neuralgia” (n = 278; 4.68%), “back pain” (n = 258; 4.35%).

Serious cases represented only 4.16 % (n = 247) of all Herpes Zoster cases and were significantly less frequent than serious non-cases ($P < 0.001$). Upon AE development, 1139 (19.19%) patients visited the emergency room and a total of 2.182 (36.77%) cases resolved at the time of reporting. We were able to retrieve the time frame between vaccination and AE onset for 5,616 cases: median time to VZV reactivation was 8 days (IQR: 2-19).

Ranked by the absolute number of reports, the highest number of VZV reactivations was reported for Pfizer-BioNTech (n = 3,263; 54.99% of total cases), while Moderna and Janssen were reported in 2,348 cases (39.57%) and 323 cases (5.44%), respectively. Cases that reported concomitant pharmacological treatment at time of AE onset were 3,688. Though this parameter revealed a higher prevalence among cases compared to non-cases (62.15% vs. 49.79%; $P < 0.001$), only 430 (7.25% of total VZV cases) patients were exposed to drugs that could potentially concur in the occurrence of VZV reactivation: 194 of them were undergoing immunotherapy and 257 were taking oral, parenteral, or inhaled glucocorticoids.

Based on the number of COVID-19 vaccine doses administered in the USA between 12/13/2020 and 12/03/2021 (Pfizer: 548,578,240; Moderna: 361,897,609; Janssen: 33,849,124), we estimated the following VZV reactivation incidence: 0.59 cases per 100,000 doses for Pfizer-BioNTech, 0.65 cases per 100,000 doses for Moderna and 0.95 cases per 100,000 doses for Janssen.

3.1.2. HSV reactivation cases

With regard to the HSV reactivation, we retrieved 273 cases: patients had a mean age of 49 ± 15 years and females represented 83.15% of cases, which were more prevalent than non-cases ($P < 0.001$). Chronic conditions affected 224 (82.05%) patients, while prior SARS-CoV-2 infection occurred in 8 (2.93%) cases, 115 (42.12%) patients reported at least an allergy, and prior vaccination AEs in 12 (4.40%) cases, but never a previous HSV reactivation.

PTs used to report HSV reactivation were: "Herpes Simplex" (n = 223; 81.68%), "Herpes Simplex reactivation" (n = 21; 7.69%), "Herpes Simplex test positive" (n = 25; 9.16 %), "genital Herpes Simplex" (n = 6; 2.20%), "ophthalmic Herpes Simplex" (n = 6; 2.20%), "Herpes Simplex encephalitis" (n = 4; 1.46%), "Herpes Simplex gastritis" (n = 1; 0.37%), "Herpes Simplex meningoencephalitis" (n = 1; 0.37%), and "Herpes Simplex pharyngitis" (n = 1; 0.37%). The other most commonly recorded PTs were the following: "condition aggravated" (n = 67; 24.54%), "fatigue" (n = 39; 14.29%), "pyrexia" (n = 39; 14.29%), "headache" (n = 35; 12.82%), "pain" (n = 31; 11.36%), "chills" (n = 25; 9.16%), "pain in extremity" (n = 16; 5.86%), "blister" (n = 12; 4.40%), "arthralgia" (n = 11; 4.03%), "lymphadenopathy" (n = 11; 4.03%).

Serious HSV reactivations represented 6.59% (n = 18) of total HSV cases and 10.62% (n = 29) patients visited the emergency room after AE occurrence; however, 42.12% (n = 115) of them recovered at time of reporting. Time to onset for HSV reactivation was available for 263 cases and showed a median time to HS infection occurrence of 3 days (IQR: 1-12) after COVID-19 vaccination.

Pfizer-BioNTech was held responsible for HSV reactivation in 151 cases (55.31% of total cases), followed by Moderna in 107 cases (39.19%) and Janssen in 15 cases (5.49%). Concomitant medication was administered in 197 cases and was more frequently reported among cases compared to non-cases (72.16% vs. 49.90%; $P < 0.001$): 17 of them (6.23% of total HSV cases) could potentially exacerbate or facilitate HSV reactivation, as 6 patients were taking immunosuppressive agents and 11 anti-inflammatory steroids.

The reporting rate estimated for HSV reactivation was of 0.03 cases per 100,000 doses for Pfizer-BioNTech, 0.03 cases per 100,000 doses for Moderna and 0.04 cases per 100,000 doses for Janssen.

3.2. Case/non-case analysis

Results of disproportionality analysis for each vaccine are shown in Table 2.

Pfizer-BioNTech revealed to be significantly correlated to VZV reactivation reporting (ROR = 1.51; 95% CI = 1.19-1.92), though its increased reporting frequency compared to the others vaccines was very small, while

241 an ROR < 1 was found for Moderna (ROR = 0.74; 95% CI = 0.58-0.94) and Janssen (ROR = 0.65; 95% CI =
242 0.38-1.09).

243 The estimated ROR for HSV reactivation reporting was found significant for the Pfizer-BioNTech vaccine
244 (ROR = 1.52; 95% CI = 1.20-1.93), whereas no SDR was found for Moderna (ROR = 0.73; 95% CI = 0.57-
245 0.93) or Janssen (ROR = 0.64; 95% CI = 0.38-1.08). The limited number of cases was liable for the wider CIs,
246 compared to VZV RORs.

247 **4. Discussion**

248 In the setting of post-marketing surveillance, the investigation of spontaneous reporting system databases is a
249 valuable tool that has a critical role in detecting rare or unexpected patterns of AE unlikely to be recognized
250 in pre-marketing clinical trials. In this context, our investigation of the VAERS revealed that Herpes Zoster or
251 Simplex reactivations in COVID-19 vaccines recipients have been reported over 6,000 times. However, the
252 number of cases retrieved amounts to approximately 1% of total COVID-19 vaccines AE reports. As compared
253 to VZV reactivation cases, the generally lower number of HSV reactivations may be due to the fact that these
254 patients do not usually seek medical care, therefore precluding reporting by healthcare professionals [61].
255 Estimated incidence was close to 0.1 case per 100,000 doses but should be interpreted taking into account the
256 latest evidence on Herpes prevalence, according to which Herpes Zoster is experienced by approximately 30%
257 of US citizens during their lifetime and more than 1.2 million individuals annually, while HSV-1 has an
258 estimated incidence of 1.1% and 2 of 1.6% [76–78]. These latter findings are mainly based on a global and
259 regional HSV incidence estimation for 2016 in people aged 15-49 and another study investigating HSV
260 prevalence in US citizens aged 14-49 in 2015–2016: both these studies found that prevalence increased with
261 age and was higher in females. These data highlight the wide diffusion of these infections; therefore, the
262 preliminary evidence emerged from our study does not suggest a safety concern attributable to COVID-19
263 vaccines at this time.

264 On that note, an Israeli study compared rates of Herpes Zoster among individuals vaccinated with the Pfizer-
265 BioNTech vaccine to unvaccinated individuals through an historical-cohort study conducted in a huge health
266 maintenance organization. No association was found (151 cases versus 141 cases; RR = 1.07; 95% CI: 0.85-
267 1.35), thus providing further reassuring data regarding the safety of COVID-19 vaccines [79].

268 No robust evidence has yet emerged on Herpes new onset following COVID-19 vaccination and, generally,
269 vaccine-induced Herpes reactivation is quite rare. Psichogiou et al. retrieved a total of 1,653 reports of VZV-
270 related complications in the VAERS recorded from July 1990 to March 2021, after exclusion of COVID-19
271 and varicella vaccines [44]. This issue highlights the fact that Herpes reactivation trigger is probably inherent
272 in the peculiar activation of the immune system induced by COVID-19, which is mimicked by its vaccines to
273 a certain extent. Patients affected by COVID-19 often experience a cytokine storm, with the considerable
274 release of many proinflammatory cytokines, including interleukin 6 (IL-6), interleukin 12 (IL-12) and tumor
275 necrosis factor-alfa (TNF-α) [80]. Meanwhile, SARS-CoV-2 has also the tendency to induce

immunosuppression characterized by a functional impairment of CD4+ lymphocytes T, and a quantitative decrease in monocytes, eosinophils, and particularly CD3+ and CD8+ T cells [15,81–86]. This imbalance in the immune system may represent the rationale for the increased susceptibility to Herpes reactivation in COVID-19 patients, since the disease-induced lymphopenia may allow VZV and HSV to evade cellular-mediated immunity and reactivate [87]. This hypothesis is corroborated by available evidence on the increase of VZV incidence among HIV-positive patients with as CD4+ T cell counts decrease, stressing the relevance of T-cell immunity in maintaining Herpes viruses latency [88,89]. Furthermore, Yu et al. via bioinformatic analysis of COVID-19- and VZV-associated genes observed that both infections are associated with the differentiation of naive CD4+ T cells into T helper 17 (Th17) cells. These lymphocytes secrete IL-17A, IL-21, and IL-22, thus promoting inflammatory processes with neutrophils recruitment [90]. Accordingly, lymphocytes isolated from COVID-19 and VZV patients have been demonstrated to secret more IL-17 [91,92]. These findings suggest that COVID-19 might induce excessive Th17 differentiation, which increases the circulating level of IL-17A, which in turn triggers VZV reactivation and the subsequent risk of Herpes zoster. Conversely, although vaccinated individuals do not manifestly suffer from lymphopenia or massive cytokine release, the likely mechanism behind Herpes reactivation following SARS-CoV-2 vaccination could be linked to the vaccine-induced polarization of the immune system towards a T cell response.

Sahin et al. have observed that vaccination with mRNA vaccines induces a humoral and cellular adaptive immunity through an extensive cellular response with S-specific CD8+ T cell and CD4+ T cells, leading to a significant production of interferon-γ [93]. This strong CD8+/CD4+ T cell responses both correlate positively with S1-binding IgG and have also been detected in pre-clinical studies [94]. It is thus postulated that, as a consequence of a massive shifting of naive CD8+ cells, VZV- and HSV- specific CD8+ cells temporarily fail to maintain control of the infection.

Our findings stress the relevance of AE reporting, since only a few case reports have been published on the matter so far and the wide cohort of cases of interest retrieved allowed us to gain precious insight on the characteristics of all patients who were reported to manifest these AEs. In fact, current evidence has suggested no overall prevalence of older patients in COVID-19 vaccine-induced VZV reactivation [37–50], by contrast we observed a higher mean age compared to non-cases. This latter finding is ultimately expected since age is a major risk factor for VZV reactivation in 90% of cases and the higher prevalence of older patients may signify that these vaccines could be a contributing risk factor but not a sufficient cause for VZV reactivation [95]. Concerning HSV reactivation, we did not find a significant difference in age distribution between cases and non-cases. The fairly low mean age we obtained for our cases (49 ± 15 years old), although partially unexpected, is consistent with the mean age (44 ± 14.6) emerged from the cross-sectional Spanish study investigating cutaneous AEs following mRNA-based COVID-19 vaccines [61]; and with two out of the three case-reports describing HSV reactivation following Comirnaty inoculation, which were aged 42 and 29, respectively [59].

The currently available evidence on this specific vaccine/AE combination found a median of 5 days for the occurrence of symptoms, in line with our findings. However, while patients described in the literature developed symptoms following either the first or the second dose, we detected five cases of VZV reactivation after both doses of Pfizer and Moderna vaccines (none of these patients was currently taking immunosuppressive agents). Overall, a small portion of our cases of interest was exposed to other medication that could act as a physiologic stressor on the patients' immune system, along with the immunomodulation induced by the vaccine, and therefore cell-mediated immunity towards VZV and HSV may have fallen below the threshold of containment and allowed the viruses reactivation.

Consistently with the fact that the majority of cases reported in the literature were related to mRNA-based vaccines, we retrieved a lower number of Janssen-induced Herpes reactivations. This could be due to the lower number of administered doses, as shown by the CDC data. Furthermore, when analyzing the relative reporting risk for each of the three FDA-approved vaccines, they were all found to have a similar SDR, though Pfizer resulted slightly more significant. In this regard, it has been speculated that the responsible for this AE occurrence is to be searched among vaccine components, but mRNA- and DNA-based vaccines share few ingredients and rely on different technologies to lead to SARS-CoV-2 S-protein production by the cell. Hence, the only shared feature is the expression of viral S-protein, which may have pleotropic effects in the host, as it has shown to favor syncytium-mediated lymphocyte elimination and conversion of lymphocytes B to macrophage-like cells with poor phagocytosis capability [96]. These effects could be responsible for misbalancing the immune response that keeps VZV dormant, but conclusive evidence is still lacking and emerging data on other DNA-based vaccines, such as the AstraZeneca/Oxford vaccine, will be pivotal in shedding light on the pharmacological mechanism behind this AE [97].

4.1. Strengths and limitations

AE reporting in large databases including the VAERS is limited by the heterogeneous data quality, the absence of defined diagnostic criteria, and the lack of a denominator, which hinders the estimation of absolute risk. These intrinsic limitations of VAERS were partly bypassed by selecting higher quality cases and by estimating the AE incidence through the retrieval of vaccine administration rates.

Moreover, disproportionality analysis is a statistical method that does not represent conclusive safety information for a vaccine and needs further clinical validation, since the potential association found does not imply causality.

Despite these limitations, the major strength of our analysis is the great number of reports retrieved and the subsequent possibility to corroborate current evidence regarding demographic characteristics of patients as well as AEs features, such as outcome, seriousness and time to onset through a case-level clinical review aimed at thoroughly examining the correlation between Herpes reactivation and COVID-19 vaccination. The wide cohort analyzed also allowed us to estimate the differential reporting risk based on the vaccine administered.

4.2. Conclusions

This is the first study aimed at investigating the potential association between COVID-19 vaccines and Herpes reactivation by using one of the largest spontaneous reporting system databases.

Almost all cases of interest we retrieved were of non-serious nature; moreover, the estimated incidence of Herpes reactivation following COVID-19 immunization was non-significant compared to the total number of U.S. citizens who usually suffer from these conditions. Furthermore, it is impossible to rule out the role of concurring factors, as well as the physical and emotional stress associated with acute illness and vaccination, being notorious Herpes reactivation triggers.

In conclusion, the paucity of cases we found, in view of the high number of COVID-19 vaccine doses administered, and the prevalence of Herpes reactivation among the general population, makes the potential occurrence of this adverse effect negligible from clinical and epidemiological standpoints, by supporting the good safety profile of the COVID-19 vaccination.

With the rapid and widespread distribution of COVID-19 vaccines, it is crucial that clinicians continue to monitor and report all suspect AEs in order to help to better characterize the safety profile of vaccines, which remain strongly recommended.

Author contributions

MG conceptualized and designed the study, interpreted the data drafted the manuscript, revised and approved the final manuscript as submitted. VB, GC, GM, GG, CL, and MP participated in the conceptualization and design of the study, participated in the analysis and interpretation of the data, revised the article, and approved the final article as submitted. SR and EC participated in the conceptualization and design of the study, participated in the analysis and interpretation of the data, coordinated and supervised data collection, critically reviewed the manuscript and approved the final manuscript as submitted. CC conceptualized and designed the study, interpreted the data, coordinated and supervised data collection, critically reviewed the manuscript and approved the final manuscript as submitted.

Each figure and table have been originally created for the purpose of this manuscript and has not been published previously.

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