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Dermatological adverse reactions after vaccination with BNT162b2 in a cohort of healthcare workers

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Abstract

Background The description of the skin reactions produced by the different vaccines against SARS-CoV-2 has focused on the symptoms reported by the general population. There are few studies with very different measurement methods focused on healthcare workers.

Methods A longitudinal observational study was conducted on all the healthcare workers from the Hospital Universitario San Cecilio that received vaccination against COVID-19 with BNT162b2. The recruitment period was from December 2020 to September 2021. The recommended regimen was double, with a minimum interval of 21 days between doses. All dermatological reactions reported as adverse effects of the vaccine were evaluated by the Staff of the Dermatology Unit of our center.

Results A total of 3969 healthcare workers of our center were followed. Only 0.7% of them reported dermatological adverse reactions. The most frequently reported reactions were morbilliform rash and COVID arm. In the multivariate analysis, the vaccination regimen (one dose) and the history of COVID-19 infection remained the main factors associated with the report of dermatological adverse reactions.

Conclusion The rate of dermatological adverse reactions after vaccination with BNT162b2 (Pfizer-BioNTech) is extraordinarily low. No patient required hospitalization, which supports the safety of this vaccination in a population of healthcare workers.

Introduction

In the last year, effective vaccines against SARS-CoV-2 have been rapidly developed, given the need for urgent control of the pandemic. The European Medicines Agency (EMA) authorized the use of four vaccines in its territory to date: BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), AZD1222 (AstraZeneca), and Ad26.COV2.s (Janssen). All of them proved their solvency in terms of efficacy, safety, and immunogenicity.

As for other vaccines, throughout the year 2021, their main adverse effects have been reported in clinical practice series and postauthorization trials. From a dermatological point of view, they have focused on local reactions at the injection site and generalized reactions at a distance from the injection site.

Two main registries of dermatological side effects have been published in 2021. First, the American registry[1] was based on data from 414 patients after vaccination with mRNA vaccine. In this registry, the lesions were evaluated by nondermatologist healthcare professionals. Second, the Spanish registry[2] evaluated 419 patients with a skin vaccine reaction from more than 30 hospital centers. Lesions were fully evaluated by dermatologists. The main contribution of this study was the characterization of six morphological patterns that include (1) local reactions at the injection point (COVID arm), (2) urticaria and angioedema, (3) morbilliform rash, (4) papulovesicular rash, (5) pityriasis rosea-like, and (6) purpuric rash. This registry did not consider the reactivation of preexisting skin infections (e.g., Varicella-Zoster Virus or Herpes Simplex Virus) as an independent subgroup.

Several case series on dermatological effects secondary to COVID-19 vaccines in healthcare workers have been published to date. The study presented by Durmaz et al.[3] evaluated these effects in 250 healthcare workers that received CoronaVac® employing a self-administered questionnaire. Robinson et al.[4] assessed the incidence of skin reactions after vaccination with mRNA COVID-19 vaccines in employees of the Mass General Brigham. The authors used a survey with a response rate of 83% and found that itching and rash were the most reported effects (1.9%) after the first vaccination dose.

The aim of this study was to assess the frequency and variety of dermatological reactions after the BNT162b2 vaccination reported by the hospital workers of our center.

Methods

Study design

A longitudinal observational study was conducted on all the workers of our center that received vaccination against COVID-19 with BNT162b2. The recruitment period started on December 27, 2020, (when the first doses arrived at the hospital) and ended on September 1, 2021 (end of follow-up). All the workers received the same vaccine type and vaccination schedule, which corresponded to the recommendations established by the Spanish Health Ministry for healthcare workers during the follow-up period of the study.[5] The recommended regimen was double, with a minimum interval of 21 days between doses. COVID-19 infection or a severe adverse reaction to the first dose were the only contraindications to the vaccine. The hospital workers were vaccinated voluntarily in a vaccination service specifically enabled by the hospital and managed by the Service of Preventive Medicine and Public Health of our center. Inclusion criteria involved all healthcare workers of our center who agreed to participate in the study. Exclusion criteria included workers under 18 years old and not voluntarily accepting vaccination.

Data source and variables

The research team accessed the registries of the Preventive Medicine and Public Health Service for identifying and recruiting the healthcare workers that received vaccination and for collecting the main sociodemographic data (gender, age, and occupational category). The occupational category was divided, according to the Occupational Health records of the Hospital, into the following categories: physicians, healthcare resident students (physicians, nurses, and pharmacists on training contract), nurses, auxiliary nurses, wardens, other healthcare workers (including physiotherapists, occupational therapists, pharmacists, psychologists, and health technicians such as laboratory technicians and radiodiagnostic technicians), administrative workers (including administrative personnel, management positions, and clinical documentation and admission technicians), and other nonhealthcare workers (including security personnel, kitchen workers, maintenance technicians, and cleaning staff).

Data on vaccination, reported adverse reactions, history of COVID-19 infection, and serological tests, were obtained from the electronic clinical histories with the help of the hospital's Information and Communication Technology (ICT) team. A vaccination regimen (one dose or double dose) was collected. The history of COVID-19 infection was divided into three groups as follows: infection before the first dose of the vaccine, infection during the vaccine (including workers with a positive PCR from the day of the first vaccine dose to 7 days after the second dose), and infection after vaccine (infection from 7 days after the second dose). These times were based on the immunization periods reported in the Comirnaty® technical data sheet by the European Medicines Agency.[6] During the first vaccine consultation, all the hospital workers received information on how to report adverse reactions or persistent symptoms after vaccination, and a specific telephone number was enabled for this purpose. The members of the research team collected and included these data in the medical records.

All dermatological reactions as adverse effects of the vaccine were evaluated by the Staff of the Dermatology Unit of our center.

Analyses

First, descriptive univariate analyses were performed to characterize the sample. Means and standard deviations were calculated for quantitative variables, and absolute frequencies and percentages were calculated for qualitative variables.

Second, bivariant analyses were conducted comparing the subgroup of patients that reported dermatological adverse reactions (DAR) with the subgroup of patients that did not. Chi-square tests were used for comparing qualitative variables between both groups and *t* tests for comparing quantitative variables. When the conditions for application were not met, Fisher exact test and Mann–Whitney *U* test were applied, respectively.

Third, multivariate logistic regression models were designed, and Odds Ratios (OR) for the development of DAR were calculated. Models were adjusted for gender, age, history of COVID-19, and vaccination doses.

All analyses were performed using Stata (StataCorp®, TX, USA), version 15.0.

Ethical considerations

The requirements established by the Declaration of Helsinki for research with human data were met. The research team used an anonymized database for conducting the analyses. No potentially identifiable data were used. The protocol of the study was approved by the Provincial Ethical Research Committee, Granada.

Results

Description of the sample

The cohort followed involved a total of 3969 workers of our hospital that received vaccination against COVID-19 with BNT162b2. This number represents over 95% of the total workers during the period of the study. Of them, 2902 (73.1%) were women, and the mean age was 46.4 years (standard deviation: 13.9). The most frequent occupational categories were nurses (21.0%), auxiliary nurses (16.7%), other nonhealthcare professionals (14.3%), physicians (12.5%), wardens (7.6%), and other healthcare professionals (7.6%). A total of 182 patients (4.6%)

reported any adverse reactions to vaccination, and 26 (0.7%) reported DAR.

The distribution of sociodemographic and clinical characteristics according to the presence of DAR is shown in Table 1. The main variable associated with reporting DAR was the history of COVID-19 infection ($p = 0.025$). Concretely, the presence of COVID-19 infection previous to the vaccine ($p = 0.023$) was a risk factor for reporting DAR in the bivariate analysis.

The one-dose regimen was also associated with reporting DAR ($p < 0.001$) as the presence of adverse reactions determined that some workers refused to receive the second dose.

Although gender (women reported more DAR) and professional category (physicians did not report any DAR, while nurses were the category that showed more frequency of DAR) revealed interesting tendencies, no significant results were observed.

The nondermatologic adverse reactions associated with DAR were fever ($p < 0.001$), general malaise ($p < 0.001$), arthromyalgia ($p < 0.001$), and vertigo ($p = 0.020$).

Table 2 shows the specific DAR reported in our study ($n = 26$). The morbilliform rash was the most frequent DAR ($n = 10$), followed by intense local reactions ($n = 7$), pruritus ($n = 6$), and herpes simplex reactivation in the lip area ($n = 5$).

Table 3 shows the factors associated with reporting DAR in crude and adjusted analyses. After adjusting for the main confounders in the multivariate analysis, the vaccination regimen (one dose) and the history of COVID-19 infection remained the main factors associated with the report of DAR.

TABLE 1 Sociodemographic and clinical characteristics stratified by the presence of dermatologic adverse reactions (DAR) reported

Variable	Total ($n = 3969$) *N* (%)/x (s)	DAR reported ($n = 26$) *N* (%)/x (s)	No DAR reported ($n = 3943$) *N* (%) / x (s)	*p* value
Age	46.4 (13.9)	46.7 (13.5)	46.4 (13.9)	0.902
Gender				
Women	2902 (73.1)	22 (84.6)	2880 (73.0)	0.184
Men	1067 (26.9)	4 (15.4)	1063 (27.0)	
Professional category[1]				0.123
Physician	495 (12.5)	0 (0.0)	495 (12.6)	0.053
Healthcare resident student	166 (4.2)	0 (0.0)	166 (4.2)	0.420
Nurse	833 (21.0)	8 (30.8)	825 (20.9)	0.220
Auxiliary nurse	662 (16.7)	6 (23.1)	656 (16.7)	0.381
Warden	302 (7.6)	1 (3.8)	301 (7.6)	0.717
Pregraduate health student	49 (1.2)	0 (0.0)	49 (1.2)	0.567
Other healthcare worker	300 (7.6)	3 (11.5)	297 (7.5)	0.442
Administrative	242 (6.1)	1 (3.8)	241 (6.1)	0.732
Other nonhealthcare worker	567 (14.3)	5 (19.2)	562 (14.3)	0471
Unknown	353 (8.9)	2 (7.7)	351 (8.9)	–
Vaccination regimen				
Complete (double dose)	3917 (98.7)	23 (88.5)	3894 (98.8)	0.004*
One dose[2]	52 (1.3)	3 (11.5)	49 (1.2)	
COVID-19 infection	568 (14.3)	8 (30.8)	560 (14.3)	0.025*
Infection before vaccine	451 (11.4)	7 (26.9)	444 (11.3)	0.023*
Infection during vaccine[3]	58 (1.5)	0 (0.0)	58 (1.5)	0.533
Infection after vaccine	59 (1.5)	1 (3.8)	58 (1.5)	0.324
Hospitalization	7 (0.2)	0 (0.0)	7 (1.3)	0.748
Serology tests				1.000
Positive IgG after vaccine	1399 (35.2)	11 (42.3)	1388 (35.2)	
Negative IgG after vaccine	6 (0.2)	0 (0.0)	6 (0.2)	
Unknown	2564 (64.6)	15 (57.7)	2549 (64.4)	

[1]Professional category named "other healthcare workers" included physiotherapists, occupational therapists, pharmacists, psychologists, and health technicians such as laboratory technicians and radiodiagnostic technicians, among others. The category "administrative" included administrative personnel, management positions, and clinical documentation and admission technicians. The category "other nonhealthcare workers" included security personnel, kitchen workers, maintenance technicians, and cleaning staff. The category "unknown" included workers with missing data regarding occupational categories.
[2]Professionals received only one dose for different reasons (e.g., adverse reaction to the first dose, refusal to receive the second dose, etc.).
[3]Infection during vaccine refers to workers who were infected between the first dose of the vaccine and 7 days after the second dose. Workers who were infected after this period were included in the category "infection after vaccine.".

TABLE 2 Specific dermatologic adverse reactions (DAR) to vaccination

DAR	Total (*n*)	% out of the total number of patients reporting DAR (*n* = 26)	% out of the total number of patients reporting reactions (*n* = 182)	% out of the total sample (*n* = 3969)
Morbiliform rash	10	38.5%	5.5%	0.26%
Intense local reaction (COVID arm)	7	26.9%	3.8%	0.18%
Pruritus	6	23.1%	3.3%	0.15%
Herpes simplex reactivation	5	19.2%	2.7%	0.13%
Herpes zoster reactivation	1	3.8%	0.5%	0.03%
Distal hyperpigmentation	1	3.8%	0.5%	0.03%
Generalized eczema	1	3.8%	0.5%	0.03%

The sum of individual DARs (*n* = 31) is higher than the number of workers reporting DAR (*n* = 26) because some of them reported more than one DAR simultaneously.

TABLE 3 Crude and adjusted odds ratio for the report of dermatologic adverse reactions after COVID-19 vaccination in hospital workers

Variable	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)	*p* value[1]
Gender (women)	2.03 (0.70–5.91)	1.96 (0.67–5.72)	0.216
Age (for each 1-year increment)	1.00 (0.98–1.03)	1.00 (0.98–1.03)	0.896
Vaccination regimen (one dose)	10.35 (3.00–35.62)	7.33 (1.95–27.57)	0.003
History of COVID-19 infection	2.67 (1.16–6.18)	2.63 (1.13–6.08)	0.024

[1]*p* value of the adjusted model for the presence of dermatological adverse reactions was reported. The multivariate logistic regression model was adjusted for all the variables included in the table. Reference categories for the calculation of Odds Ratios were men, two-dose regimen, and not having an antecedent of COVID-19 infection, respectively.

Discussion

This study confirms the low frequency of adverse reactions after the BNT162b2 vaccination and the wide variety of possible dermatological symptoms reported.

The associations found between DAR and other adverse reactions in previous studies (mainly fever, general malaise, and asthenia)[7] suggest that DAR after the BNT162b2 vaccine are part of a complex systemic response after vaccination, probably associated with a transitory decrease in immunity during the generation of new antibodies against COVID-19. This may justify the relatively high presence of herpes simplex reactivations (0.13% of the total vaccinated workers) and the herpes zoster reactivation of one worker (0.03%).

From a dermatological point of view, the main skin reactions that we found in our cohort of patients are intense reactions at the injection site (COVID arm). This pattern, as described by Catalá et al.,[2] is more frequent after vaccination with Moderna (mRNA-1273) and more frequent in women, in accordance with our series. This Spanish nationwide study also found an association between morbilliform rash and more severe concomitant reactions requiring hospitalization.[2] We could not confirm this association, as no patient requiring hospital admission due to adverse reactions was found in our study.

Reactivation of herpetic infection by HSV and VZV has also been reported in our series, although in a lower percentage than in other series.[1,2,4] In the longest published series,[8] 77% of VZV reactivation cases occurred after the first dose of the vaccine, with no predominance due to vaccination of mRNA of one or another commercial brand. Once again, there is a predominance of the female gender and the caucasian race. However, HSV reactivation was lower than in our series and, in this case, it was more predominant in patients who received Pfizer-BioNTech. As in our cohort, the diagnosis of both virus reactivations was clinical in all cases.

Regarding the association of previous COVID-19 infection, our adjusted analysis suggests that workers with antibodies generated from infection are more susceptible to present DAR after vaccination. The association with a one-dose regimen is invaluable, as many of the workers refused to have a second dose because of the adverse event, therefore reverse casual bias is highly probable. Finally, our bivariate analyses showed a tendency to report more DAR in women and in nurses, with no statistical differences, which should be further explored in larger studies.

This study has some limitations. First, we conducted a one-center study. However, we included >95% of the hospital workers, obtaining a high representative sample size. Second, we collected only reported adverse events. It is probable that these

data are underestimated, as many workers with less severe adverse reactions may have not reported them. Similarly, potential long-term DAR could be underrepresented as participants may not attribute them to the vaccine. Finally, time from previous COVID-19 infection to vaccination and time from vaccination to DAR were not included in the analyses, given the low number of outcomes observed. Nevertheless, these data might be considered in future larger studies. Therefore, the associations that we present should be considered cautiously.

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