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RESEARCH ARTICLE

Late Skin Reactions Associated with the Modern Vaccine

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Abstract

Summary

The infection by the SARS-CoV-2 virus and the disease generated by COVID-19 that began in 2019 in Wuhan China has had a great impact on global morbidity and mortality, which in turn led to the creation in record time of the first vaccines used in humans against coronavirus. Vaccines such as Sinovac, Janssen, AstraZeneca, Pfizer and Moderna, of which have been authorized and administered in multiple countries with really favorable results. However, late post-vaccination adverse effects have been reported in patients vaccinated especially by Moderna and Pfizer, observing a compromise at the level of the skin causing the appearance in most cases of urticaria, edema, erythema, reactivation of herpes zoster, morbilliform eruptions, among others that are undoubtedly related to the mechanisms of action of the aforementioned vaccines.

Keywords: COVID-19, dermatology, Modern, mRNA, immunization, vaccine, SARS-CoV 2.

1 | INTRODUCTION

The appearance of epidemics and pandemics is not something new in the history of humanity, however, in recent years, the human species has witnessed outbreaks, many of them mainly due to viruses, which cause alarm in public health (1) a clear example dates back to the end of 2019 where the SARS-COV2 virus began its dissemination from China and in March 2020 it was declared a pandemic due to the high death rate that it caused and that, to this day, continues to cause (2). Since January 2020 to date there have been more than 161, 824,992 cases of the COVID-19 disease caused by the SARS-CoV-2 virus and with it more than 3'357,598 deaths, also leaving multiple sequelae and economic losses (3).

Due to all this problem, and the lack of effective treatments and therapies that will cause a control of the clinical pathology, it was necessary to create vaccines that will help mitigate the mortality rate due to covid-19, within the framework of vaccines there are Several options available to the population, among those officially administered in most of the world are BioNTech / Pfizer (Comirnaty®), Moderna, AstraZeneca, Sinovac and Janssen, to achieve the coveted "herd immunity", in addition to contributing to the advancement of research on how the human immune system reacts when in contact with this virus (4).

Vaccines against Sars-Cov 2

Faced with the great impact caused by this Covid-19 virus, the WHO (world health organization) promoted the initiative to create an international COVID-NMA research plan, arising from the R&D plan, which has facilitated the assessment combined of a large number of clinical trials and evidence on prevention, treatment and vaccines against the disease, acts that have undoubtedly led to a better understanding of decision-making, progress and achievement of applying some of the vaccines that are undoubtedly essential for the control of the pandemic (5).

Among the vaccines most used by the population are RNA vaccines, recombinant proteins, viral vectors, and inactive sars cov-2 virus (Table 1). However, in Colombia, direct and indirect contracts to acquire vaccines are allowed for five laboratories: Pfizer, Astra Zeneca, Moderna, Janssen and Sinovac, which have different mechanisms to generate an immune response and different levels in the evolution of their clinical trials. In general, the efficacy of these vaccines in preventing any degree of severity of COVID 19 infection is estimated to be between 70% and 95%. However, when it comes to avoiding serious infections that require admission to the ICU or cause death, the efficacy is close to 99% (6).

Supplementary information The online version of this article (https://doi.org/10.52845/JMRHS/2021-4-11-8) contains supplementary material, which is available to authorized users.

Table 1. Vaccines used against Covid-19 disease, taken from C. Galván-Casas, A. Català and C. Munoz-Santos

Vaccine	Name / company / country	Composition	Special features	Advantage	Disadvantages
RNA vaccines	BNT162 / Comirnaty® (Pfizer® / BioNTech®, Germany, United States) mRNA 1273 (Moderna®, United States)	They contain messenger RNA (mRNA) that teaches cells to produce the protein that triggers an immune response to infection (induces ribosomal production of proteins that code for the antigen)	Reactions more adverse frequent (mRNA powerful activator immunity) Special caution in people with background of allergy and anaphylaxis Administration intramuscular	They do not have the capacity to produce disease (like those of attenuated viruses) They do not have the capacity to integrate into the host genome (like those of DNA) They generate a more intense and lasting immune response They stimulate the innate immune system. MRNA and lipid carrier act as adjuvants	Instability Difficult storage conditions Ability to stimulate the innate immune system, with the production of INF1 and eventual decrease in efficacy

Recombinant proteins	NVX-CoV2373 (Novavax®), United States	They use artificially created virus proteins, such as the protein S receptor-binding domain (RBD) protein	Obtained by genetic engineering, account with the experience of other licensed vaccines (hepatitis B, HPV, flu). They use adjuvants to enhance their effect (MATRIX-M) Intramuscular Administration	Manufacturing is easier	They generate less immune response
Viral Vectors	-Vaxzevria® (Oxford / AstraZeneca®, UK) -Ad26Cov2-S (Janssen®, United States) -Sputnik-V® (Gamaleya®, Russia)	They use another virus, modified to express a SARS-CoV-2 antigen	intramuscular administration AstraZeneca uses a chimpanzee adenovirus engineered to express protein S and disabled for in vivo replication	Storage at normal refrigeration temperature, facilitating logistics and distribution in developing countries.	Risk of loss of efficacy if neutralized by pre-existing immunity. To avoid this, they use infrequent vectors in humans or with low immunogenic capacity.
Inactivated SARS-Cov-2 viruses	-CoronaVac® (Sinovac Biotech®, China) -Covaxin® (Bharat Biotech®, India)	SARS-CoV-2 cell culture and virus inactivation by chemical or physical methods (formaldehyde, heat, or ultraviolet light)	The immune response targets proteins S, M, E, and N They use adjuvants to enhance their effect (aluminum hydroxide)	Safer than live attenuated vaccines, cannot cause disease, and generate fewer reactions	They generate less immune response Local reactions to aluminum hydroxide

In the case of Moderna's vaccine, like the vaccine developed by the pharmaceutical companies BioN-Tech and Pfizer, it is a vaccine that uses nucleic acids, specifically it is a non-replicating messenger RNA, modified with nucleosides that encode the peak glycoprotein of SARS- CoV-2 and is encap-sulated in lipid nanoparticles In addition, mRNA is encapsulated in lipid nanoparticles to protect it from degradation and favor its uptake in host cells. The target antigen is the S protein of SARSCoV-2, since it is the protein responsible for the binding and fusion of the virus with host cells. After vaccination, the mRNA instructs some cells to temporarily produce protein S and then the T and B lymphocytes of the immune system develop immune responses against protein S by recognizing it as foreign and producing neutralizing antibodies. If in the future the vaccinated person comes into contact with the virus, these anti-bodies will bind to the peak protein (protein S) of SARS-CoV-2, preventing the S protein from being used by the virus itself to bind and fuse with host cells, thus achieving their neutralization (6).

Post injection physical manifestations

All vaccines induce some level of inflammation triggered by the activation of innate immunity, that is why the imbalance of these responses can cause inflammatory reactions, which can manifest on the skin, generating certain clinical manifestations (7).

The clinical manifestations or also called "reactogenicity" usually occur primarily from inflammatory processes whose local presentation at the injection site manifests as pain, heat, redness, swelling, induration, however, it is also usually accompanied by systemic manifestations such as fever, myalgia, headache among others. (8) (9)

2 | MATERIALS AND METHODS

A detailed bibliographic search of information published since 2015 is carried out, in the databases pubmed, Elsevier, scielo, national and international libraries. The following descriptors were used: skin reactions, Modern, SARS-COV2, arm-covid. The data obtained ranges between 10,000 and 40,000 records after the use of the different keywords. The search for articles was carried out in Spanish and English, it was limited by year of publication and studies published since 2015 were used.

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3 | RESULTS

In general, most of the adverse skin manifestations expected after vaccination with COVID are mild and are related to the presence of acute signs such as erythema (redness) and local edema (inflammation) in the area surrounding the inoculation; which are not usually worrisome from the clinical point of view due to the common presence of these in the rest of vaccines, and which also usually persist a maximum of three days until their complete resolution without health intervention, anaphylactic reactions can also be generated (anaphylactic and / or allergic reactions) that are usually <0.02%, have greater clinical importance and generally these usually appear between 15-30 minutes post-immunization, therefore, they do not fall into the picture of late manifestations, however, it is relevant its mention in the dermatological processes triggered by the Moderna vaccine (10).

In addition, a great variety of cutaneous manifestations have been described that coincide with vaccination by Moderna and with no other apparent cause; the most frequently reported reaction is the appearance of erythematous and edematous plaques of different sizes in the area where it is received the vaccine (11) (12). The first published cases appeared 7 to 10 days after the first dose of Moderna®, which was initially attributed to a hypersensitivity reaction to the polyethylene glycol contained in the vaccine. However, in another series, the intradermal test with polyethylene glycol polysorbate only showed positivity in one patient with a reaction that occurred only after the second dose (13). Another study supports a delayed or T-cell-mediated hypersensitivity reaction as the cause, based on the histopathological picture, which showed the presence of superficial perivascular and peripollicular lymphocytic infiltrates with

dispersed mast cells and eosinophils. It is important to know how to differentiate between mediate and immediate reactions; Angioedema, pruritus and redness are found in skin reactions that usually appear immediately, those manifestations that appear after 3 days to 14 days later (late reactions), present a variable percentage depending on the type of vaccine (84%, Moderna and 17% Pfizer), within this framework are included erythromelalgia (in fingers and toes) and those morbilliform, urticarial, maculopapular eruptions, lichen planus, erythema multiforme and reactivations of herpes zoster, however, they are well known. has described that 43% of patients usually present this type of manifestations or other less common ones such as herpes simplex or rashes similar to pityriasis rosea after the first dose of modern medicine (14) (15) These data are corroborated by the recent publication of 414 reactions after the Moderna® and Pfizer® vaccines reported by different health professionals, through the SARS-CoV-2 skin manifestations registry of the American Academy na of Dermatology. No serious reactions were found and half of the patients with reactions after the first dose did not present them after the second dose. Another manifestation described after this vaccine is the covid arm (16) (17) (Figure 1), which manifests itself in the form of large plaques, between 10-25 cm, with an erythematous-edematous appearance that appears in the injection site after 7 days from inoculation, clinically not considered serious for health However, it is necessary to refer to Dermatology for its study (18). Additionally, the American Academy of Dermatology suggests different reactions observed both after the vaccination of the first dose and after the inoculation of the second dose, such as erythromelalgia and perniosis (19), the most common manifestations being ”arm-covid”, urticarial eruptions and the reactivation of a shingles. The arm-covid This is the appearance of erythematous and edematous plaques of different sizes, in the area where the vaccine was received. These eruptions have been described with other vaccines, such as the combined pneumococcal vaccine (20). In one study, the covid-arm was reported as the most frequent (mRNA-1273, Moderna, 61.9%), where the majority of reactions to the Moderna vaccine were described in women (90.5%) (21). which is related to the results of Jacobson, Mark A., et al.

Reporting that late-onset itchy and erythematous injection site rashes af-ter administration of the SARS-CoV-2 mRNA-1273 vaccine, lasting up to 1 week, commonly occur in women after the first dose. In addition, a skin punch biopsy demonstrated a largely perivascular lympho-cytic infiltrate with few epidermal changes accompa-nied by interstitial neutrophils and eosinophils. Mi-croscopic findings resemble urticarial hypersensitiv-ity dermatitis (Figure 2). (22). In the study by Larson, Valerie, et al. They found two injection site reac-tions showing a mixed cell infiltrate with eosinophils and a spongiotic dermatitis with eosinophils. Three biopsy specimens were from generalized eruptions showing interface changes consistent with an exanthematous drug reaction. Three other biopsy specimens revealed a predominantly spongiotic pattern, consistent with eczematous dermatitis. In addition, they observed vascular injury of small vessels in two samples, which were diagnosed as urticarial vasculitis and leukocytoclastic vasculitis, respectively. They also had two cases of bullous pemphigoid (23).

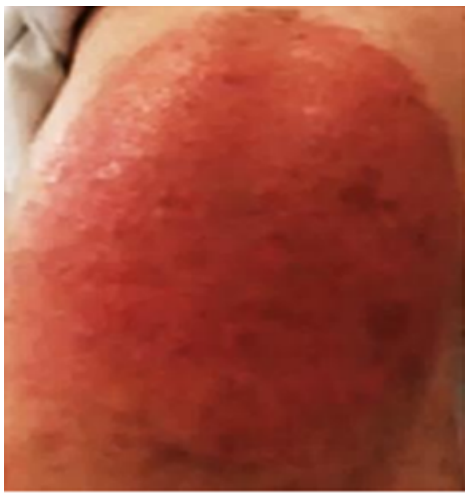

FIGURE 1: Erythema-edematous plaque "Arm Covid" (Source image modified from: HolaDoctor.com)

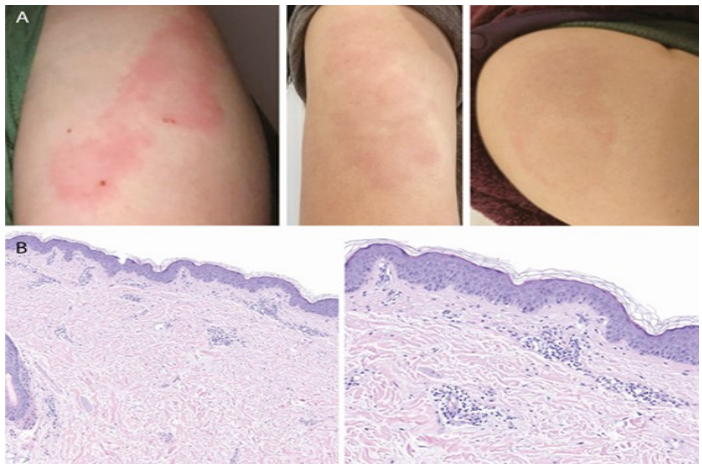

FIGURE 2: Late injection site reactions after the first dose of mRNA-1273.

In addition, painful purple spots may appear on the abdomen, buttocks and lower extremities accom-panied by flaccid blisters (Figure 3), 5 days after the administration of the Moderna vaccine, as oc-curred in a 66-year-old male patient with a clinical history. Together with the histopathological results, the diagnosis is a bullous pharmacological reaction with characteristics of Stevens-Johnson syndrome, since histopathology showed full thickness, epider-mal necrosis and very little lymphocytic inflammation (24). Another case presentation reports a 60-year-old woman who after receiving mRNA-1273 vaccination on skin examination indicated a sudden-onset, significant generalized rash that spread rapidly throughout the body. The rash was brown to red, purpuric, and not whitening (Figure 4). She also had a 5x5 cm bruise on her left shin. The rash was localized to the entire body, including the trunk, all four extremities, predominantly the forearms, shins, and chest wall. They described the rash as a rash that is not itchy or painful (25).

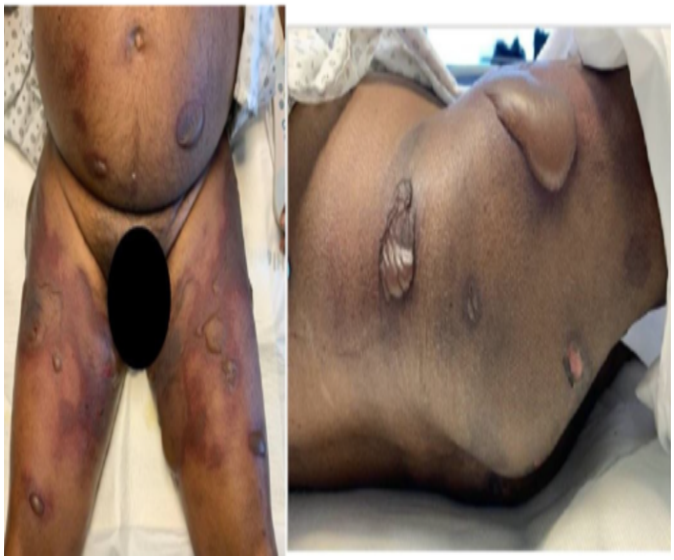

FIGURE 5: Skin reaction of blistered and painful purplish patches after vaccination with Moderna.

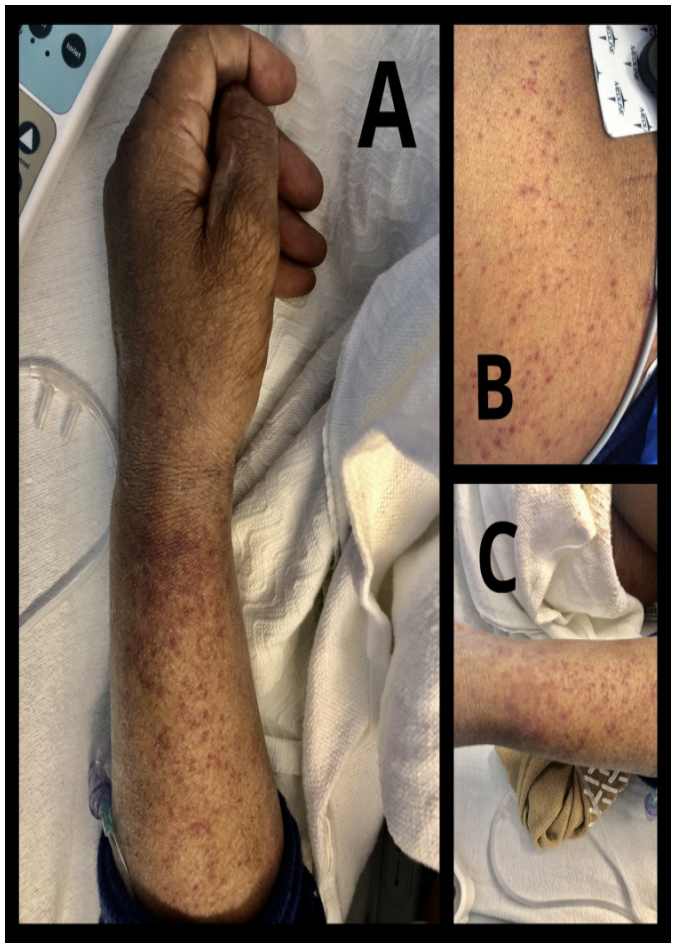

FIGURE 3: Papular rash on the right left (A), the chest (B) and the left leg (C) after receiving the COVID-19 mRNA-1273 vaccine.

Vaccines against COVID-19 have been shown to cause systemic reactions similar to infection with the SARS-CoV-2 virus. In a study by Mc Mahon it was discovered that from December 2020 to February 2021, 414 skin reactions occurred to the COVID-19 mRNA vaccines from Moderna (83%) and Pfizer (17%), with large local reactions delayed more com-mon, followed by local reactions at the injection site, urticarial eruptions and morbilliform eruptions, then found that 43% of patients with reactions to the first dose experienced recurrence with the second dose (26), in the same way According to drug surveillance studies carried out by the CDC (Center for Diseases Control) and the FDA in November 2020, after hav-

ing administered the first doses to 1,893,360 people, 175 cases with severe allergic reactions including anaphylaxis were reported that, although It is not a late reaction, it is clinically considered important to determine (27), in fact, On December 15, a 32-year-old health worker from Alaska, who had no allergies As known, he presented an anaphylactic reaction within 10 minutes after receiving the first dose of the vaccine, since then, much attention has been paid to the dermatological reactions that vaccines may have after their administration (28). In a study carried out by Wei N this year, a series of cases of late middle-aged women with no dermatological history with the presence of late dermatological lesions such as pruritic erythematous eruptions, non-squamous erythematous patches and pruritus with the presence of erythematous plaque with mild scales which were manifested in 4/4 of the cases in a time interval of 7-10 days post vaccination with modern in its first dose (29). In fact, the mRNA-1273 vaccine clinical trial reported late injection site reactions (onset after day 8) in 0.8% of participants after the first dose and 0.2% after. Of the second dose, which explains and supports the results in the study by Wei N (30). In an analysis by Fernández Nieto, of 4775 subjects who underwent vaccination with BNT162b2 mRNA, a total of 864 general side effects (18.1%) were recorded, the mean age was 43.2 years (range 19-72) and 721 (83.4%) of the patients were female, however, a delayed injection site injury was observed that was present in 103 subjects (2.1%), either after the first dose (49/103, 47.6%) or after the second dose (54/103, 52.4%) (31)

4 | DISCUSSION

The COVID-19 pandemic presents an unprecedented challenge given the rapid pace of scientific discoveries and clinical data generated by the number of people rapidly infected with SARS-CoV-2. Based on experimentation with the SARS and MERS viruses, most of the vaccines that have been developed against SARS-CoV-2 are based on protein S, which is the protein that binds to the cell receptor and mediates fusion activity of membranes. Therefore, prior to mass administration, preclinical information was based on the theory that a CoV vaccine could theoretically cause adverse effects due to a phenomenon known as Antibody Dependent Enhacement of Infectivity (ADEI) (32). It is considered that the reduction in the creation time of the vaccine, together with the imminent need to obtain it and the decrease in bioethical standards, will definitely result in a greater probability of unpredictable side effects caused by the vaccine (33). The Centers for Disease Control and Prevention (CDC) of the United States (USA) have documented a total of 157 reactions in practically 6 million administered doses of mRNA vaccines, which is equivalent to an overall incidence of less than 0.003%. , of which only 1 in 5 would meet criteria for anaphylaxis. Thus, although the incidence of anaphylaxis from this type of vaccine is very low (5 for every 1. 000.000 doses administered), it is 5 times higher than that reported with vaccines against other viral agents (34). The first report from the Spanish Agency for Medicines and Health Products confirms that there have been no serious effects in vaccinated patients, and this is very important in the field of vaccination. Most of the side effects are mild systemic or self-limited local reactions, such as fever and headache that appear in the first 24-48 hours and resolve in 2 to 3 days. Reactions appear to be more common with the second dose and in people younger than 55 years (35). Clinical trials have shown that the main cutaneous manifestations are categorized as rosacea, cellulitis, urticaria, masculopapular rash, angioedema and dermal filler edema in the case of Moderna (36) Moderna's vaccine contains an excipient called tromethamine (or tromethamine) also present in radiological contrast media and other medical devices including some NSAIDs and cosmetics that has recently been implicated in an immediate hypersensitivity reaction after the administration of gadolinium, which are probably the causes of cutaneous manifestations (37). In addition, the most common adverse reactions were injection site pain, fatigue or tiredness, headache, muscle pain, chills, joint pain, redness, vomiting, fever, and swelling at the site of infection and in most cases of mild or moderate intensity. Moderna's vaccine has a rare and characteristic adverse reaction called "Covid Arm" (erythrodermic skin reaction associated with lymphodenopathy). The most serious adverse reactions

it presents are anaphylaxis (severe allergic reaction) and acute peripheral facial paralysis, which were classified as very rare adverse reactions and their frequency could not be determined with the clinical trial (38). In a study in Spain where patients with skin reactions within 21 days were included After any dose of the vaccines, we found that the cutaneous manifestations according to the Modern vaccine were urticaria, Covid arm, vesicular papule, pityriasis rosea, morbilliform, purpuric and reactivating herpetiform lesions (39). One study collected cases of skin manifestations after vaccination with Moderna (83%) and Pfizer (17%) where 414 cases were recorded. Delayed large local reactions were the most common, followed by local injection site reactions, urticarial eruptions, and morbilliform eruptions. Forty-three percent of patients with reactions to the first dose experienced recurrence with the second dose (40). Differences in the biodistribution and pharmacokinetics of mRNAs, as well as the properties of the different lipid nanoparticles, could also play a role in the pathogenesis of this late-onset reaction; however, the pharmacokinetic data of both vaccines in humans are scarce (41). Hypersensitivity reactions are being reported to these vaccines (5.0 and 2.8 cases per million doses for the Pfizer-BioNTech and Moderna vaccines, respectively) and these rates are higher than those of other similar vaccines (1.3 cases per million doses). As in the case of a 39-year-old woman with a history of allergic rhinitis who received dose 1 of the Moderna vaccine and developed chest and neck urticaria within 15 minutes (42). In some people, a localized skin reaction with erythema and swelling occurs on the upper arm at the injection site, known as a ”COVID arm.” It is considered a delayed-type hypersensitivity reaction and occurs mainly in individuals after vaccination with the Moderna vaccine, but rarely with other mRNA vaccines (43). Delayed skin reactions have also been observed around the ChAdOx1 nCoV-19 vaccine injection site. Demonstrated in the reporting of 4 cases of patients with no history of hypersensitivity reactions to drugs or vaccines, where the reactions began with erythematous swelling and other systemic symptoms (44). A case report of a 66-year-old male patient reports that after receiving the second dose of Moderna, he developed fever, myalgias, and malaise within 24 hours, accompanied by a painful rash with blisters on the torso, arms, and legs (45). . Even a series of 16 cases reported late localized skin reactions that developed in a median of 7 (2-12) days after receiving the Modern COVID-19 vaccine. These reactions occurred at or near the injection site and were described as pruritic, painful, and edematous pink plaques. Of the participants who had a reaction to the first dose of vaccine (15 of 16 patients), the majority (11 patients) developed a similar localized reaction at the injection site to the second dose of vaccine. The majority (10 patients) also developed the second reaction earlier compared to the first dose reaction. (46) The Centers for Disease Control and Prevention currently recommends that patients who experience immediate hypersensitivity reactions, including hives, within 4 hours of receiving the COVID-19 vaccine postpone the second dose until after consulting with an allergist-immunologist (47).

5 | CONCLUSION

The results found suggest that after administration of the mRNA-1273 vaccine, skin reactions predominate in women and in patients over 60 years of age. Where the most frequent reactions are ”arm-covid” and urticaria. Being these common, benign adverse events that can be resolved in a week, which suggests not stopping the vaccination. However, the follow-up of an immuno-allergist is essential, especially with patients with systemic clinical manifestations.

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