

Cutaneous Reactions Following COVID-19 Vaccination: A Review of the Current Literature

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Abstract: The outbreak of coronavirus disease 2019 (COVID-19) represented a new worldwide challenge, strongly impacting on the global economy, overall health and lifestyle. Since then, several strategies have been adopted to contain the widespread of infection. Among these, vaccination is currently the most important measure to fight against the pandemic. However, several concerns such as slower-than-hoped-for rollout, the hurried approval with limited data, the mechanism of action (in particular mRNA-based), and the uncertain duration of protection they afforded were initially raised. Moreover, even if cutaneous reactions have been rarely reported in clinical trials, global mass vaccination showed several dermatologic reactions not initially recognized, leaving dermatologists to decide how to diagnose and treat them. In this scenario, dermatologists should be ready to promptly recognize these clinical manifestations. Thus, the aim of this manuscript is to review current literature on cutaneous reactions following COVID-19 vaccination, particularly inflammatory dermatological diseases, in order to help clinicians to better understand these dermatological conditions and to provide an extensive overview of all the vaccine-related skin manifestations.

Keywords: cutaneous reactions, COVID-19 vaccinations, side effects

Introduction

The outbreak of coronavirus disease 2019 (COVID-19) represented a new worldwide challenge, strongly impacting on the global economy, overall health and lifestyle.¹ Since then, several strategies have been adopted to contain the widespread of infection.^{2,3} Dermatologists played a key role during the pandemic, fighting against several challenges such as cutaneous reactions caused by COVID-19 disease, the hesitancy on the efficacy and safety of conventional treatment and biologic drugs in this period, the worsening of several dermatosis due to the wearing of personal protection equipment and the introduction of a new lifestyle.⁴⁻⁶ Indeed, the “stay-at-home” policy and the restrictive measures adopted by the Italian Government during the COVID-19 pandemic period strongly affected the quality of life.⁷ In addition, COVID-19 restriction measures affect the epidemiology of infectious diseases and skin cancers.^{5,8-10}

Among the developed public health strategies to control the spread of COVID-19, vaccination is currently the most important measure to fight against the pandemic. However, several concerns such as slower-than-hoped-for rollout, the hurried approval with limited data, the mechanism of action (in particular mRNA-based), and the uncertain duration of protection they afforded were initially raised.^{11,12} Fortunately, worldwide vaccination campaign was a success, showing to be the most effective weapon to prevent and control COVID-19 epidemic, disease progression, hospitalization and mortality.¹³

According to the WHO COVID-19 dashboard accessed on 11 September 2021, more than 608 million confirmed cases of COVID-19 have been reported, with almost 6.51 million deaths.¹⁴ Nowadays, licensed vaccines for COVID-19, use nucleic acid-based vaccination platforms, such as viral vector platforms, messenger ribonucleic acid and inactivated virus.¹³

Four vaccines have been approved by the European Medicines Agency (EMA): 2 mRNA-based vaccines (Pfizer/BioNTech; BNT162b2 and Moderna; mRNA-1273) and 2 viral-vector-based vaccines (AstraZeneca; AZD1222 and Johnson & Johnson; Ad26.COV2.S).¹⁵ However, other vaccines have been approved in other countries such as

“CoronaVac” (Sinovac), “Sputnik V” (Gamaleya Research Institute), and “Convidecia” (CanSino Biologics).¹³ Currently, more than 5.3 billion people have received at least one dose of COVID-19 vaccine.¹⁶

Similar to other drugs, some people reported mild-to-moderate adverse events following vaccination, including fatigue, headache, diarrhea, redness or pain at the injection site, fever, muscle aches, chills.^{17–19} Fortunately, most of the side effects are limited, with a duration of few days.^{17–19}

Even if cutaneous reactions have been rarely reported in clinical trials, global mass vaccination showed several dermatologic reactions not initially recognized, leaving dermatologists to decide how to recognize and treat them. In particular, a wide spectrum of cutaneous reactions has been reported.²⁰ However, the significance of these reactions is still unknown. In this scenario, dermatologists should be ready to promptly recognize these clinical manifestations, which should be considered in personalized medicine.^{21,22}

Thus, the aim of this manuscript is to review current literature on cutaneous reactions following COVID-19 vaccination, particularly inflammatory dermatological diseases, in order to help clinicians to better understand these dermatological conditions and to provide an extensive overview of all the vaccine-related skin manifestations.

Materials and Methods

For the current review, literature research was carried out on the PubMed, Embase, Cochrane Skin, Google Scholar, EBSCO and MEDLINE databases (until September 11, 2022). Research was performed by using the following keywords: “COVID-19”, “vaccination”, “vaccine”, “cutaneous”, “side effects”, “adverse events”, “skin manifestations”, “mRNA”, “viral-vector”, “Pfizer/BioNTech”, “BNT162b2”, “Moderna”, “mRNA-1273”, “AstraZeneca”, “AZD1222”, “Johnson & Johnson”, “Ad26.COV2.S”, “atopic dermatitis”, “psoriasis”, “lichen planus”, “bullous disease”, “pemphigus”, “pemphigoids”, “hidradenitis suppurativa”, “urticaria”, “rash”, “herpes”, “pityriasis rosea”, “chilblains”, “vitiligo”, “erythematous eruption”, “alopecia”, “local-injection”, “angioedema”, “eczema”. Analyzed articles included meta-analyses, reviews, letter to editor, real-life studies, case series and reports. The most relevant manuscripts were considered. Studies were selected if they provided information on cutaneous reactions following COVID-19 vaccination with BNT162b2, mRNA-1273, AZD1222 and Ad26.COV2.S, both first and second doses, if applicable. Cutaneous reactions following other vaccines, or the booster dose were excluded. Articles regarding skin reactions reported in clinical trials or with a limited number of cases were excluded. Manuscripts reporting local injection site reactions, both immediate and delayed, rash or unspecified cutaneous eruption and delayed inflammatory reactions to dermal hyaluronic acid filler were not considered. Moreover, articles where the vaccine leading to cutaneous reaction was not specified were excluded. Thus, the research was refined by reviewing the texts and the abstracts of collected articles. The bibliography was also reviewed to include articles that could have been missed. Only English language manuscripts were considered. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors. Details of the included studies are reported in [Table 1](#).

Results

A total of 1922 reports were initially found searching literature. Subsequently, 523 articles and 71 manuscripts were excluded since they were duplicates and in non-English languages, respectively. Then, literature review was refined following inclusion and exclusion criteria. Finally, a total of 183 articles involving 456 patients were selected in the current review. Main findings are summarized in [Table 1](#).

Several cases of new onset or exacerbation of inflammatory skin diseases have been reported ([Figure 1](#)) as well as the type of vaccine causing these reactions has been investigated ([Figure 2](#)). As regards psoriasis, a total of 98 reports on psoriasis following COVID-19 vaccination were reported.^{23–54} In particular, flare of pre-existing disease and new-onset disease were reported in 81 and 17 cases, respectively. Moreover, several phenotypes of psoriasis were reported, with plaque subtype as the most frequent. Of note, even if biological treatments showed excellent results in terms of effectiveness and safety in psoriasis management,^{55–58} they seem to reduce the possibility of disease worsening following vaccination, without nullifying the risk. Moreover, the effectiveness of COVID-19 vaccines in patients undergoing treatment with biologics is debated.^{59,60}

Table I Main Cutaneous Reaction Following COVID-19 Vaccination

Cutaneous Reaction	Cases	Authors and Number of Cases	Overall Reported Cases by Vaccines
New-onset psoriasis	17	Tran et al ²³ (3), Ouni et al ²⁴ (2), Nagrani et al ³⁵ (1), Song et al ⁴⁶ (1), Frioui et al ⁴⁹ (1), Cortonesi et al ⁵⁰ (1), Lehmann et al ⁵¹ (1), Elamin et al ⁵² (1), Wei et al ⁵³ (1), Lamberti et al ⁵⁴ (1), Romagnuolo et al ²⁵ (1), Ruggiero et al ²⁶ (1), Ricardo et al ²⁷ (1), Pesqué et al ²⁸ (1).	BNT162b2: 10 mRNA-1273: 3 AZD1222: 3 Ad26.CO2: 1
Flare of psoriasis	81	Huang et al ²⁹ (15), Sotiriou et al ³⁰ (14), Koumaki et al ³¹ (12), Megna et al ³² (11), Wei et al ⁵³ (6), Ruggiero et al ²⁶ (4), Durmaz et al ³³ (2), Tran et al ³⁴ (2), Piccolo et al ³⁶ (2), Bostan et al ³⁷ (1), Nagrani et al ³⁵ (1), Pavia et al ³⁸ (1), Durmus et al ³⁹ (1), Fang et al ⁴⁰ (1), Krajewski et al ⁴¹ (1), Trepanowski et al ⁴² (1), Mieczkowska et al ⁴³ (1), Lopez et al ⁴⁴ (1), Perna et al ⁴⁵ (1), Tsunoda et al ⁴⁷ (1), Nia et al ⁴⁸ (1), Pesqué et al ²⁸ (1).	BNT162b2: 43 mRNA-1273: 17 AZD1222: 21 Ad26.CO2: 0
Cutaneous lichen planus	16	New-onset: Merhy et al ⁶² (1), Camela et al ⁶³ (1), Kato et al ⁶⁹ (1), Diab et al ⁷⁰ (1), Zagaria et al ⁷¹ (1), Awada et al ⁷² (1), Picone et al ⁷³ (1), Hlaca et al ⁷⁴ (1), Zengarini et al ⁷⁵ (1), Masseran et al ⁷⁶ (1), Gamonal et al ⁶⁴ (1), Alrawashdeh et al ⁶⁵ (1), Shakoei et al ⁶⁶ (1). Flare: Hiltun et al ⁶⁷ (1), Herzum et al ⁶⁸ (1), Hlaca et al ⁷⁴ (1).	BNT162b2: 8 mRNA-1273: 1 AZD1222: 7 Ad26.CO2: 0
New-onset atopic dermatitis/eczema	7	Rerknimitr et al ⁷⁷ (3), Holmes et al ⁷⁸ (1), Leasure et al ⁷⁹ (1), Bekkali et al ⁸⁰ (1), Larson et al ⁸¹ (1).	BNT162b2: 3 mRNA-1273: 1 AZD1222: 3 Ad26.CO2: 0
Flare of atopic dermatitis/eczema	14	Potestio et al ⁸² (11), Leasure et al ⁷⁹ (1), Niebel et al ⁸³ (1), Larson et al ⁸¹ (1).	BNT162b2: 8 mRNA-1273: 3 AZD1222: 3 Ad26.CO2: 0
Hidradenitis suppurativa	6	Martora et al ⁹⁰ (5), Alexander et al ⁸⁹ (1).	BNT162b2: 2 mRNA-1273: 3 AZD1222: 1 Ad26.CO2: 0
Urticaria	98	Magen et al ⁹⁴ (39), Potestio et al ⁹⁵ (15), Rerknimitr et al ⁷⁷ (12), Riad et al ⁹⁶ (10), Sidlow et al ⁹⁷ (3), Peigottu et al ⁹⁸ (2), Niebel et al ⁸³ (2), McMahon et al ⁹⁹ (2), Holmes et al ⁷⁸ (2), Fernandez-Nieto et al ¹⁰⁰ (2), Bianchi et al ¹⁰¹ (2), Corbeddu et al ¹⁰² (2), Baraldi et al ¹⁰³ (1), Choi et al ¹⁰⁴ (1), Patruno et al ¹⁰⁵ (1), Burlando et al ¹⁰⁶ (1), Thomas et al ¹⁰⁷ (1).	BNT162b2: 71 mRNA-1273: 12 AZD1222: 15 Ad26.CO2: 0
Alopecia areata	24	Scollan et al ¹⁰⁹ (9), Babadjouni et al ¹¹⁰ (3), Rossi et al ¹¹¹ (3), Chen et al ¹¹² (2), Abdalla et al ¹¹³ (1), Gamonal et al ¹¹⁴ (1), Ho et al ¹¹⁵ (1), Su et al ¹¹⁶ (1), Gallo et al ¹¹⁷ (1), May Lee et al ¹¹⁸ (1), Essam et al ¹¹⁹ (1).	BNT162b2: 14 mRNA-1273: 4 AZD1222: 6 Ad26.CO2: 0
Pemphigus vulgaris	26	Martora et al ¹²¹ (7), Zou et al ¹²² (3), Gui et al ¹²³ (2), Rouatbi et al ¹²⁴ (2), Aryanian et al ¹²⁵ (1), Koutlas et al ¹²⁶ (1), Knechtel et al ¹²⁷ (1), Ong et al ¹²⁸ (1), Yıldırıncı et al ¹²⁹ (1), Singh et al ¹³⁰ (1), Norimatsu et al ¹³¹ (1), Agharbi et al ¹³² (1), Almasi-Nasrabadi et al ¹³³ (1), Corrá et al ¹³⁴ (1), Solimani et al ¹³⁵ (1).	BNT162b2: 15 mRNA-1273: 6 AZD1222: 5 Ad26.CO2: 0
Pemphigoids	40	Maronese et al ¹³⁷ (21), Maronese et al ¹³⁸ (3), Hali et al ¹³⁹ (3), Gambichler et al ¹⁴⁰ (2), Shanshal et al ¹⁴¹ (1), Desai et al ¹⁴² (1), Fu et al ¹⁴³ (1), Alshammari et al ¹⁴⁴ (1), Hung et al ¹⁴⁵ (1), Pauluzzi et al ¹⁴⁶ (1), Dell'Antonia et al ¹⁴⁷ (1), Pérez-López et al ¹⁴⁸ (1), Agharbi et al ¹⁴⁹ (1), Young et al ¹⁵⁰ (1), Nakamura et al ¹⁵¹ (1).	BNT162b2: 29 mRNA-1273: 5 AZD1222: 6 Ad26.CO2: 0

(Continued)

Table 1 (Continued).

Cutaneous Reaction	Cases	Authors and Number of Cases	Overall Reported Cases by Vaccines
Morphea	9	Paolino et al ¹⁵² (4), Antoñanzas et al ¹⁵³ (2), Oh et al ¹⁵⁴ (1), Metin et al ¹⁵⁵ (1), Aryanian et al ¹⁵⁶ (1).	BNT162b2: 6 mRNA-1273: 1 AZD1222: 2 Ad26.CO2: 0
Pityriasis rosea	40	Temiz et al ¹⁵⁸ (14), Ramot et al ¹⁵⁹ (6), Martora et al ¹⁶⁰ (3), Khattab et al ¹⁶¹ (2), Cyrenne et al ¹⁶² (2), Valk et al ¹⁶³ (1), Buckley et al ¹⁶⁴ (1), Wang et al ¹⁶⁵ (1), Shin et al ¹⁶⁶ (1), Bostan et al ¹⁶⁷ (1), Leerunyakul et al ¹⁶⁸ (1), Cohen et al ¹⁶⁹ (1), Dormann et al ¹⁷⁰ (1), Bin Rubaian et al ¹⁷¹ (1), Fenner et al ¹⁷² (1), Marcantonio-Santa Cruz et al ¹⁷³ (1), Abdullah et al ¹⁷⁴ (1), Carballido et al ¹⁷⁵ (1).	BNT162b2:33 mRNA-1273: 4 AZD1222: 2 Ad26.CO2: 1
Herpes zoster	55	Naoum et al ¹⁷⁸ (22), Agrawal et al ¹⁷⁹ (12), Monastirli et al ¹⁸⁰ (7), Furer et al ¹⁸¹ (6), Vastarella et al ¹⁸² (3), Palanivel et al ¹⁸³ (2), Vallianou et al ¹⁸⁴ (1), Jiang et al ¹⁸⁵ (1), You et al ¹⁸⁶ (1), Tanizaki et al ¹⁸⁷ (1).	BNT162b2:31 mRNA-1273: 5 AZD1222: 19 Ad26.CO2: 0
Chilblains-like/peño	12	Russo et al ¹⁸⁸ (3), Paparella et al ¹⁸⁹ (1), Davido et al ¹⁹⁰ (1), Lopez et al ¹⁹¹ (1), Pileri et al ¹⁹² (1), Piccolo et al ¹⁹³ (1), Pérez-López et al ¹⁹⁴ (1), Cameli et al ¹⁹⁵ (1), Kha et al ¹⁹⁶ (1), Lesort et al ¹⁹⁷ (1).	BNT162b2:9 mRNA-1273: 2 AZD1222: 1 Ad26.CO2: 0
Vitiligo	11	Kaminetsky et al ¹⁹⁸ (1), Militello et al ¹⁹⁹ (1), Singh et al ²⁰⁰ (1), Nicolaidou et al ²⁰¹ (1), Flores-Terry et al ²⁰² (1), Bukhari et al ²⁰³ (1), Uğurer et al ²⁰⁴ (1), Ciccarese et al ²⁰⁵ (1), López Riquelme et al ²⁰⁶ (1), Okan et al ²⁰⁷ (1), Caroppo et al ²⁰⁸ (1).	BNT162b2: 7 mRNA-1273: 3 AZD1222: 1 Ad26.CO2: 0

Abbreviations: BNT162b2, Pfizer mRNA-BNT162b2; mRNA-1273, Moderna mRNA-1273; AZD1222, AstraZeneca-Oxford AZD1222; Ad26.CO2, Johnson & Johnson Ad26.CO2.S.

Lichen planus is a chronic, inflammatory, autoimmune disease with an unknown pathogenesis.⁶¹ To date, 13 cases of new-onset cutaneous lichen planus and 3 cases of cutaneous lichen planus exacerbation have been reported.^{62–76} Like psoriasis, also cases of new onset and flare of atopic dermatitis or eczema have been reported (7 and 14, respectively).^{77–83} However, there is not a clear correlation with clinical phenotypes.⁸⁴ Moreover, undergoing treatment with dupilumab does not seem to prevent the possibility of a flare of the disease, even if its efficacy and safety have been largely demonstrated.^{85,86} No data of atopic dermatitis worsening in patients undergoing treatment with janus kinase inhibitors are available.^{87,88} Concerning hidradenitis suppurativa, there are currently few cases of new-onset disease (n = 1)⁸⁹ or disease exacerbation (n = 5).⁹⁰ However, patients with hidradenitis suppurativa are not at higher risk for any COVID-19 vaccine-related adverse outcomes.^{91,92}

Urticarial rashes are the second most common cutaneous reaction following COVID-19 vaccination reported, following local injection site reactions, such as “Covid-arm”.⁹³ Globally, 98 cases of urticarious eruptions following COVID-19 vaccination have been collected in our review,^{77,78,83,94–107} also during treatment with omalizumab.¹⁰⁸

Alopecia areata has been reported following COVID-19 vaccination.^{109–119} The largest study on 77 patients developing alopecia areata (39) or a worsening of the disease (38) has been reported by Nguyen et al. Unfortunately, it is not possible to correlate alopecia areata development and the type of vaccine.¹²⁰

Regarding bullous disorders, a total of 26 cases of pemphigus vulgaris have been reported following COVID-19 vaccination,^{121–135} with several implications in treatment and management.¹³⁶ Moreover, 40 cases of pemphigoids have been described.^{137–151}

Regarding other cutaneous diseases developed following COVID-19 vaccination, 9, 40, 55, 12 and 11 cases of morphea,^{152–157} pityriasis rosea,^{158–177} herpes zoster,^{178–187} chilblains,^{188–197} and vitiligo^{198–208} have been reported.

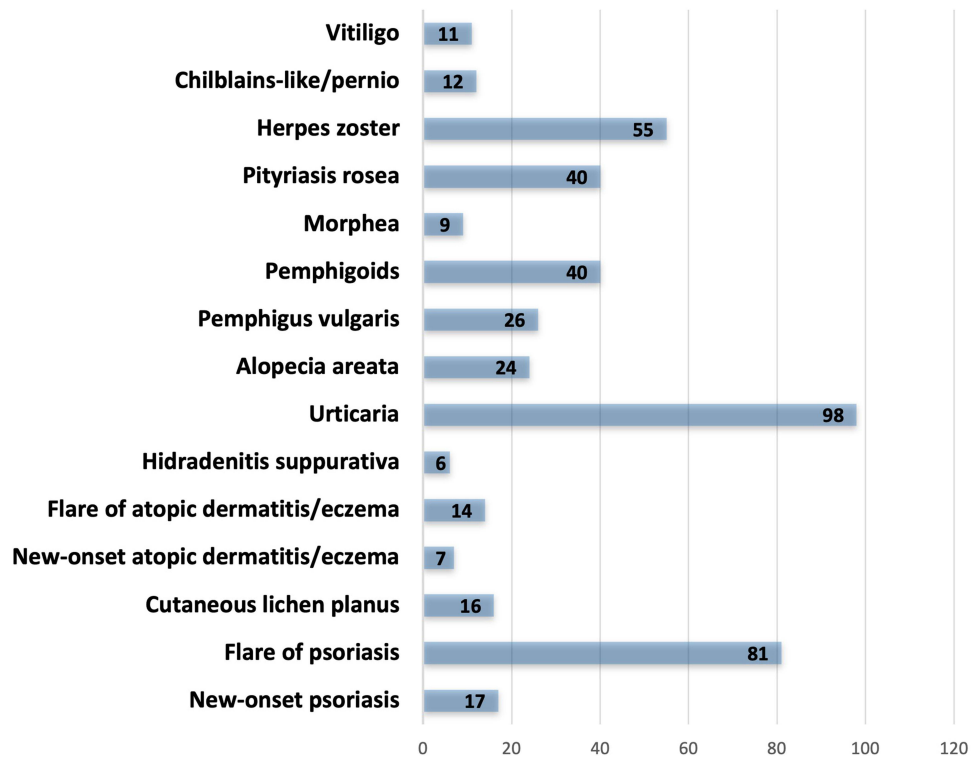


Figure 1 Cutaneous reactions investigated and number of cases.

Note: the different number of administered vaccines may explain the difference between the number of skin reactions following mRNA or viral vector-based vaccines.

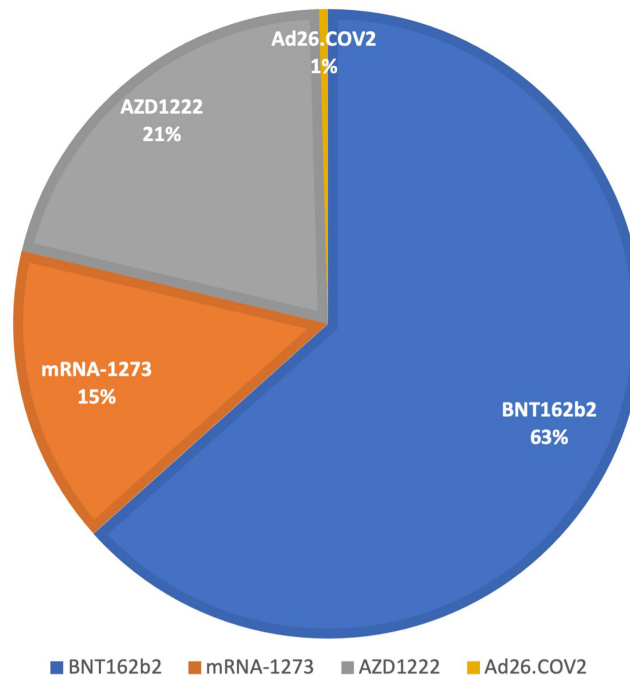


Figure 2 Percentage of vaccine types investigated that cause cutaneous reactions.

Abbreviations: BNT162b2, Pfizer mRNA BNT162b2; mRNA-1273, Moderna mRNA-1273; AZD1222, AstraZeneca-Oxford AZD1222; Ad26.COVS, Johnson & Johnson Ad26.COVS.

Finally, several other dermatoses have been described, even if data are limited. Among these, we want to highlight pityriasis rubra pilaris, leukocytoclastic vasculitis, morbilliform rash, livedo racemosa, fixed drug eruption, erythema annulare centrifugum, granuloma annulare, fascial neutrophilic eruption, annular rash, Henoch-Schönlein purpura, dermatomyositis, regression of viral wart, Raynaud phenomenon, eruptive angiomatosis, lichen striatus, pityriasis lichenoides et varioliformis acuta, Rowell's syndrome, acrocyanosis, ... suggesting that a wide type of dermatoses may be triggered by COVID-19 vaccination.^{209–221} However, most of these are limited to 1 or 2 case reports.

Discussion

COVID-19 pandemic revolutionized daily clinical practice. Indeed, several strategies were adopted to contain the spreading of the infection.²²² Dermatologists had to change their clinical routine in order to avoid the reduction in detection and treatment of several conditions, particularly skin cancer.^{223–227} Among these, teledermatology allowed physicians to continuously assist patients' dermatologic conditions with excellent results in terms of treatment adherence and clinical outcomes.^{228–230} Vaccination campaign is the most important strategy showing excellent results in terms of safety and effectiveness.^{231,232} Indeed, it allowed to reduce the severity and the impact of COVID-19 pandemic. However, several skin diseases induced or exacerbated by COVID-19 vaccination have been reported. Fortunately, most of them were mild and self-limited, not requiring medical attention. In our review, we highlighted several cutaneous reactions following COVID-19 vaccination such as psoriasis, atopic dermatitis, bullous disease, etc. Even if not specifically investigated, local injection-site reaction was the commonest cutaneous vaccine-related adverse event reported. Of note, cutaneous reactions were reported following vaccination with both mRNA and viral vector-based vaccines, suggesting that the pathogenetic mechanism underlying the cutaneous reaction is not directly related to the vaccine mechanism of action itself.⁹⁹ Certainly, further studies are needed to understand pathogenetic mechanisms linking cutaneous reaction and COVID-19 vaccination in order to identify "at-risk" subjects and to adopt preventive measures.

Of note, among the articles reviewed in our work, the diagnosis of cutaneous reactions was confirmed by histopathological examination in most of the cases. However, a shared immune process was not found assessing the histological reports.

Overall, mRNA vaccines, particularly BNT162b2, seem to be most commonly associated with cutaneous reactions. However, mRNA vaccines were previously authorized, produced and administered worldwide. Thus, the different number of administered vaccines may explain the difference between the number of skin reactions following mRNA or viral vector-based vaccines. Further epidemiological studies will clarify if the percentage of cutaneous reactions following vaccination is significantly higher in one of the two types of vaccines, with clinical implications.

To sum up, our review analyzed several dermatoses exacerbated or developed following COVID-19 vaccination. However, the temporal association between the administration of the vaccine and the development of skin reaction may be casual.

As regards the dose of vaccination, cutaneous reactions were reported following both the first and the second dose of vaccine. Furthermore, skin reactions following both the doses in the same patient have been reported as well. In our opinion, clinicians should be prepared also to cutaneous reaction following the booster dose.²³³

Strengths and Limitations

Main strengths of our review are the systematic method during the literature research and the high number of analyzed article and cutaneous reactions analyzed. Main limitations should be discussed. First, only the four vaccines approved by EMA have been considered. Moreover, several articles reporting registry-based studies did not allow the direct correlation between type of vaccine and cutaneous reaction. Finally, dermatological conditions developed following COVID-19 vaccination are usually mild and patients do not seek for medical attention.

Conclusion

With the worldwide advance of vaccination programs, several cutaneous reactions have been reported. Fortunately, the percentage of these adverse events is extremely low if compared with the number of vaccines administered. In our opinion, other cutaneous reactions following COVID-19 vaccination will be reported. Moreover, the pathogenetic mechanisms linking vaccination and skin reactions should be clarified. Clinicians should keep in mind the possibility

of the exacerbation of the new onset of several dermatoses following vaccination in order to promptly recognize and differentiate vaccine-induced cutaneous manifestations from other clinical entities. Certainly, vaccination should not be discouraged.

Disclosure

The authors report no conflicts of interest in this work.

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