Influence of Covid-19 vaccination on immune-mediated skin diseases

To the Editor,

Covid-19 vaccines are either replication-deficient adenoviral vector vaccines or nanoparticle-formulated RNA encoding the SARS-CoV-2 spike protein that produces the vaccine protein by the inoculated cell. The cutaneous adverse events from these vaccines are recorded in large registries. They include local or delayed injection site reactions, urticarial, maculopapular, morbilliform, or papulovesicular rashes and chilblain-, livedo- and vasculitis-like lesions, swelling at the site of cosmetic fillers, varicella-zoster or herpes simplex flares, and pityriasis rosea-like reactions.

Here, we analyse the effect of Covid-19 vaccination on immune-mediated skin diseases (IMSD) based on 10 patients seen in our outpatient clinics (Table 1) and recent publications. The mean age of our cohort was 51.9 years (range 31–81 years), and six patients were female. IMSD developed with a minimal latency of 3 days after the first vaccination and between 5 hours and 2 weeks after the second vaccination. Seven patients showed an exacerbation of a pre-existing skin disease, which so far had been well controlled with topical therapy only. Three of them (patients 1, 2 and 3) developed flares of guttate psoriasis (Fig. 1a, patient 2 according to Table 1). In patient 4, plaque psoriasis evolved into severe generalized pustular psoriasis (GPP) that improved upon treatment with an IL-17A antibody (Fig. 1c,d,e). Psoriasis exacerbations occurred predominantly after the second vaccination and could be controlled by systemic therapy. The current literature reports on 45 cases of plaque or guttate psoriasis and GPP in association with Covid-19 vaccination. Ten of these cases (22.2%) had new-onset psoriasis. As in our patients, psoriasis occurred mainly after the second dose (71%, n = 32) and less frequently after both doses (9%, n = 4), with a mean latency of 14.4 days and a mean PASI of 11.0 (n = 29). The mean age at manifestation was 60.3 years, and 25 (55.6%) of the patients were male. Plaque psoriasis was the most common type (60%, n = 27), followed by GPP and guttate psoriasis (9%, n = 4 each).

In patients 5 (Fig. 1f) and 6, a previously chronic stable hand eczema was aggravated by acute, dyshidrotic episodes. Bullous pemphigoid (BP) flared up in patient 7 (Fig. 1b) after each vaccination, and newly developed after the first vaccination in patient 9 (Fig. 1h), with a severe relapse after the second and third vaccination. We also identified more than 26 cases of vaccination-related BP in the literature. Other newly induced skin diseases in our patients were plaque psoriasis (patient 8) and chilblain-like/gloves and socks-like skin lesions (PPGSS, patient 10, Fig. 1i). Cases of dyshidrotic eczema and PPGSS have previously been observed only after Covid-19 infection but not vaccination.

Also, 5 of the 10 patients had undergone booster immunization. Patient 7 received the same vaccine, patient 9 received another mRNA vaccine and both developed a relapse of BP again. Patients 8 and 10 changed vaccines and IMSD did not recur. Patient 6 received the same vaccine as a booster under systemic therapy of alitretinoin and did not suffer an aggravation (Table 1). Patients 4 and 5 refused booster vaccination.

Based on the cases presented here, we conclude that Covid-19 vaccination may either aggravate or newly induce IMSD. Free intracellular RNA may cause a pronounced activation of innate immune mechanisms by binding to intracellular Pattern Recognition Receptors (PRRs) sensing viral RNA. Activation of innate immunity is required for the development of various immune-mediated skin diseases. The effect on immune-mediated skin diseases is therefore likely due to the vaccination-induced innate immune activation in susceptible individuals. Although a direct relationship is hard to prove, the temporal association, the emerging number of reports, and the fact that the aforementioned manifestations have also been associated with SARS-CoV-2 infection, strongly suggest a causal link. Accordingly, patients with a pre-existing IMSD should be informed about a possible disease exacerbation following vaccination. Treatment of induced exacerbation should be chosen in such a way that it does not interfere with the vaccine efficacy and temporarily avoid drugs such as methotrexate or systemic glucocorticoids. Patients who already are under systemic treatment for IMSD should stop the immunobiological or immunosuppressive treatment 2–4 weeks before and restart it again 2–4 weeks after the vaccine. Despite the risk of IMSD exacerbations, patients must not be discouraged to take the vaccination. Heterologous immunization might increase levels of neutralizing antibodies and prevent IMSD from relapsing after booster vaccination.

Acknowledgement

The patients provided their consent to have their cases reported.
Table 1: Summary of immune-mediated skin diseases in association with SARS-CoV-2 vaccination in 10 patients

| Patient | Age, gender | Vacci- | Pre-existing SD | Duration pre-existing SD | Treatment of pre-existing SD at presentation | IMSD Related to vaccine dose | Latency vaccine-IMSD | Vaccine (1st, 2nd, 3rd) | Clinical presentation | Histopathology | Treatment/ outcome |
|---------|-------------|--------|-----------------|--------------------------|-----------------------------------------------|----------------------------|----------------------|---------------------|---------------------|-----------------|-------------------|
| 1       | 66 y, F     | Gutta- | Chronic plaque psoriasis | 20 y | None | 1, 2 | 3 d | 1. + 2. BNT162b2 3. mRNA-1273 | Small, scaly plaques on trunk, PASI 13,5 | Not performed | TCS, UVB phototherapy, improved with etanercept |
| 2       | 59 y, F     | Guttat- | Chronic plaque psoriasis | 5 m | TCS | 2 | 2 w | 1. + 2. BNT162b2 3. mRNA-1273 | Small, scaly plaques on trunk and extremities, PASI 16,5 | Not performed | TCS, UVB phototherapy, improved with ciclosporin |
| 3       | 35 y, F     | Guttat- | Chronic plaque psoriasis | 17 y | None | 1, 2 | 1 w, 1 d | 1. + 2. BNT162b2 3. mRNA-1273 (refused) | Small, scaly plaques on trunk and extremities, PASI 9,6 | Not performed | TCS, UVB phototherapy, improved with dimethyl fumarate |
| 4       | 31 y, F     | Guttat- | Guttate psoriasis | 2 m | None | 1, 2 | 2 d | 1. + 2. BNT162b2 3. mRNA-1273 (refused) | Pustules and erythematous plaques PASI 33,0 | Not performed | TCS, UVB phototherapy, improved with ciclosporin |
| 5       | 34 y, F     | Guttat- | Guttate psoriasis | 20 y | None | 1, 2 | 1 w | 1. + 2. BNT162b2 3. mRNA-1273 | Small, tense, clear, fluid-filled vesicles | Not performed | TCS, UVB phototherapy, improved with dimethyl fumarate |
| 6       | 72 y, M     | Dyshidri- | Chronic plaque psoriasis | 67 y | TCS | 1, 2 | 2 w | 1. + 2. BNT162b2 3. mRNA-1273 | Small, tense, clear, fluid-filled vesicles, fissures | Not performed | Dimethyl fumarate, resolved by day 7 |
| 7       | 54 y, M     | Dyshidri- | Guttate psoriasis | 2 m | TCS | 1, 2 | 2 w | 1. + 2. BNT162b2 3. mRNA-1273 | Subepidermal bullous, papules, and vesicles | Not performed | TCS, OCS, Topical PUVA, resolved by week 4 |
| 8       | 56 y, M     | Dyshidri- | Guttate psoriasis | n/a | TCS | 1, 2 | 2 w | 1. + 2. BNT162b2 3. mRNA-1273 | Erythematous scaly plaques on preexisting sites, palms and soles, PASI 7,2 | Not performed | TCS, OCS, Topical PUVA, resolved by week 6 -8 weeks |
| 9       | 81 y, F     | Bullous Pemphigoid | Chronic plaque psoriasis | n/a | TCS | 1, 2, 3 | 1 w | 1. + 2. BNT162b2 3. mRNA-1273 | Tense, clear, fluid-filled bullous and vesicles | Perivascular neutrophilic and eosinophilic infiltration in the dermis with leucocytoclastosis, interstitial oedema |
| 10      | 31 y, M     | Bullous Pemphigoid | Chronic plaque psoriasis | n/a | TCS | 1, 2, 3 | 2 w | 1. + 2. BNT162b2 3. mRNA-1273 | Erythematous bullous and vesicles | Calcinosis cream, resolved with belzutimab |

*F, female; M, male; SD, skin disease; IMSD, immune-mediated skin disease; BP180/230, antibodies against bullous pemphigoid antigen 180/230; DIF/IIF, direct/indirect immunofluorescence analysis; PASI, psoriasis area and severity index; PUVA, psoralen plus UVA treatment; TCS/OCS, topical/oral corticosteroids; d, days; w, weeks; m, months; y, years.

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Figure 1  Representation of individual patients from Table 1. (a) Patient 2 with typical manifestation of plaque psoriasis. (b) In Patient 7, BP was confirmed by linear deposition of IgG and C3 along the basal membrane zone in immunohistology and BP180 or BP230 antibody titres of 130.7 U/mL or 1.4 U/mL. (c–e) Patient 4 had chronic plaque psoriasis (c) that developed into a first GPP episode 5 d after the first vaccination (d) followed by severe aggravation 7 d after the second dose of BNT162b2 which was finally resolved by treatment with an IL-17A antibody (ixekizumab) (e). (f) Patient 5 developed a pruritic eruption of small vesicles (arrow) on both palms. (h) Patient 9 presented with tense blisters (arrow) on the trunk and extremities diagnosed as de-novo BP. (i) In Patient 10, examination revealed erythematous pruritic plaques on both hands and feet resembling purpuric gloves and socks syndrome.
Conflicts of interest
None declared.

Funding sources
None.

Data availability statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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DOI: 10.1111/jdv.18388