

## COMMENTARY

## Skin adverse reactions to Sars-CoV-2 vaccination: a relevant responsibility issue for dermatologists

A total of 7.71 billion doses of Sars-CoV-2 vaccines have been administered, covering approximately the 53% and 70% of the world and European population respectively.<sup>1</sup> Consequently, an increasing number and type of skin adverse reactions to vaccination have been reported, soliciting the interest of the dermatological community. In the manuscript published in this issue of the Journal of European Academy of Dermatology and Venereology entitled “Cutaneous findings following COVID-19 vaccination: review of world literature and own experience”, Gambichler et al. provide a clear overview on cutaneous adverse events associated with Sars-CoV-2 vaccination and discuss their possible pathogenesis.<sup>2</sup> Briefly, the most frequent cutaneous findings are the local injection-site reactions, which are generally mild and self-limiting.<sup>2</sup> Severe reactions, such as anaphylaxis, urticaria and angio-oedema, are much more rare and likely related to type I hypersensitivity reaction to selected vaccine components (i.e. polyethylene glycols and polysorbate 80).<sup>2</sup> A wide range of delayed type IV hypersensitivity reactions have been reported, including the “COVID-19 arm”, maculo-papular exanthema, erythema multiforme, filler reactions, BCG-itis and radiation-recall dermatitis.<sup>2</sup> Moreover, flares of pre-existing dermatoses, such as psoriasis, atopic dermatitis and chronic urticaria, have been consistently documented. Indeed, mRNA-based vaccines can directly activate plasmacytoid dendritic cells resulting in the production of type I IFNs and multiple proinflammatory cytokines activating T cells and triggering psoriasis in susceptible individuals. The generation of autoreactive lymphocytes and cross-reactive antibodies due to molecular mimicry between Sars-CoV-2 spike protein and endogenous human cross-reactive antigens may be involved in the pathogenesis of other adverse reactions, including vasculitis, lupus erythematosus, bullous pemphigoid and vaccine-induced immune thrombocytopenia.<sup>2,3</sup> Finally, functional angiopathies (i.e. chilblain-like lesions and erythromelalgia) and the reactivation of viral conditions, as pityriasis rosea-like rashes and herpes zoster, have been described but their causal relationship remains controversial.<sup>2</sup>

We believe that dermatologists play a crucial role in establishing such association and requiring a skin biopsy for histopathological confirmation in selected cases. The causal association

between vaccination and adverse cutaneous reaction is still an open issue because specific diagnostic criteria are missing. As for other adverse drug reactions, the case ascertainment usually relies on plausible temporal sequence, strength and biological consistency. The recurrence of the adverse reactions following a subsequent vaccine dose may strengthen the causal association but raises a question about the safety of the following administrations, also considering that a periodical booster dose will be likely required for maintaining the immunity against the virus. Although patients with mild or moderate cutaneous reactions could undergo a further dose of vaccine, dermatologists may be concerned about a possible legal revenge in case of relapse of such reactions whether contraindication was not endorsed. In selected cases, the administration of a different type of vaccine and/or a prophylactic premedication with antihistamines and oral or topical glucocorticoids may be reasonable.<sup>4</sup>

For patients with immune-mediated inflammatory diseases, such as psoriasis and atopic dermatitis receiving conventional or biologic disease modifying anti-rheumatic drugs, the vaccination against Sars-CoV-2 is recommended. Although patients receiving methotrexate (likely also cyclosporine) could have a reduced response to mRNA Sars-CoV-2 vaccines, it may still provide some degree of protection against the infection. However, it is debated whether methotrexate treatment should be withheld in vaccination candidates and for how long. In contrast, treatment with biological agents does not induce lower antibody response and can be continued safely.<sup>5,6</sup>

In conclusion, skin adverse reactions to Sars-CoV-2 vaccination could rarely occur, and they are generally mild and self-limiting. Dermatologists will play an important role in establishing the real association between skin reaction and vaccination, addressing their pathogenetic mechanisms and the open issues still present.<sup>2,4</sup> The responsibility of making the casual association is trading off with the need of each individual to receive repeated doses of the vaccine. There is, thus, an urgent need to internationally establish recommendations on how to advice at best doctor and patients.

### Conflicts of interest

None.

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