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SHORT COMMUNICATION

COVID-19 Vaccination Safety in Patients who have had SARS-CoV-2-induced Chilblains

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Chilblains have been widely reported during the COVID-19 pandemic (1–6). The aetiological role of COVID-19 is debated, since most patients who had chilblains did not produce anti-SARS-CoV-2 antibodies, but the immunological hypothesis of a strong interferon response to SARS-CoV-2 can explain both the seronegativity and the mild or absent systemic signs of COVID-19 (6). Finally, association between chilblains and SARS-CoV-2 exposure has been strongly suggested in 2 case-control studies (7, 8). Following widespread vaccination against COVID-19, rare cases of post-vaccine chilblains have also been observed (9–11). However, how individuals who have previously developed chilblains associated with SARS-CoV-2 exposure react to these vaccines has not been studied. No specific recommendation has been made regarding the number of vaccine doses required in this population. In addition, the risk of systemic reactions or acral manifestations is unknown. The aim of this study was therefore to describe outcomes following vaccination in a cohort of patients who have previously developed SARS-CoV-2-induced chilblains.

METHODS

We recently reported the 1-year-follow-up of 82 individuals referred for chilblains between March and May 2020 in 5 University Hospitals in Western France (Rennes, Brest, Nantes, Angers and Tours) (12). Of these patients, 15 declined to be contacted again, and 67 were surveyed. They were sent a questionnaire on 17 September 2021, and were asked to report on their reactions to the COVID-19 vaccine. When needed, further details were obtained by teleconsultation. The study cohort was compared for systemic reactogenicity with the participants aged 16–55 in the phase 3 Pfizer/BioNTech trial (13).

RESULTS

A total of 54 (81%) individuals answered the questionnaire. Five (9.3%) had refused to be vaccinated. Five (9.3%) had received a single dose of vaccine, including 1 with positive serology following chilblains, 2 with PCR-positive COVID-19, and 2 for whom the family doctor decided that one dose was sufficient because of SARS-CoV-2-induced chilblains. Among the 49 individuals who were vaccinated, respectively, 43 (88%), 3 (6%) and 3 (6%) received the Pfizer/BioNTech, Moderna, and AstraZeneca vaccines, in line with vaccine availability in France. The median (interquartile range) age was 29 years (18–38), and 31 were women (63%).

Systemic adverse events were reported for the first and second dose, respectively: pain at injection site 57% and 43%, fatigue 39% and 50%, fever 8% and 18%, chills 4% and 14%, muscle pain 33% and 36%, joint pain 6% and 11%, and headache 16% and 18%. Regarding the Pfizer/BioNTech vaccine, individuals who had developed SARS-CoV-2-induced chilblains had similar reactogenicity to the participants aged 16–55 years in the vaccine trial (**Table I**) (13). In addition, 1 man, age 38 years, without comorbidity, visited the emergency department for tachycardia occurring 7 days after the first dose, without pericarditis or myocarditis, which resolved spontaneously and did not recur after the second dose. Regarding cutaneous adverse events, 1 woman, age 43 years, reported maculopapular exanthema of the trunk on day 2 after the second dose, which began to fade after 24 h. No individual reported relapse of chilblains. However, 3 patients (a 15-year-old woman, a 12-year-old boy, and a 66-year-old man) reported erythromelalgia of the feet from day 1 or day 2 after the first or the second injection, lasting 1 week following the Pfizer/BioNTech vaccine ($n=2$), and 1 month following the AstraZeneca vaccine ($n=1$). No other acral manifestations (acrocyanosis, Raynaud phenomenon) were reported.

DISCUSSION

Similar proportions of systemic adverse events following COVID-19 vaccination were observed among individuals who had previously developed SARS-CoV-2-induced chilblains compared with the participants in the vaccine trial. No relapse of chilblains was observed following vaccination. However, 3 individuals (6.1%) reported erythromelalgia. This reaction was reported in a registry-based study for 19 cases out of 803 cutaneous reactions following COVID-19 vaccines (14). In Vigibase, the WHO's global pharmacovigilance database, on 10 November 2021, 46 cases of erythromelalgia were reported following COVID-19 vaccines, including 25, 13, 6 and 1 cases for the Pfizer/BioNTech, AstraZeneca, Moderna, and Janssen vaccines, respectively. This is a very rare reaction to vaccines, already described for 2 patients after influenza and hepatitis B vaccines. Persistent erythromelalgia has also been reported following SARS-CoV-2-induced chilblains (12, 15).

This study is important, since individuals who have previously developed SARS-CoV-2-induced chilblains can be especially reluctant to undergo vaccination. Some patients may be confident in their efficient antiviral im-

Table I. Systemic reactogenicity of Pfizer/BioNTech COVID-19 vaccine among individuals who have previously had SARS-CoV-2-induced chilblains, compared with participants included in the vaccine trial.

	First dose		Second dose	
Symptoms	Previously developed SARS-CoV-2 induced chilblains $n=43$	Participants aged 16–55 years included in the phase 3 Pfizer/BioNTech trial[a]	Previously developed SARS-CoV-2 induced chilblains $n=40$	Participants aged 16–55 years included in the phase 3 Pfizer/BioNTech trial[a]
Pain at injection site	61%	83%	48%	78%
Fatigue	40%	47%	53%	59%
Fever	7%	4%	20%	16%
Chills	5%	14%	15%	35%
Muscle pain	35%	21%	38%	37%
Joint pain	5%	11%	13%	22%
Headache	16%	42%	20%	52%

[a]10,889 participants, age range 16–55 years.

mune response having resulted in the occurrence of chilblains, while SARS-CoV-2 variants can cause more severe infections than the initial strain. Others may be afraid of a particularly severe reaction to a vaccine, due to the vascular damage and inflammation induced by SARS-CoV-2 exposure. Several patients in the study cohort contacted us for reassurance before agreeing to vaccination. Reporting on the safety of COVID-19 vaccines in this population could contribute to tackling vaccine reluctance.

However, the generalizability of these results is limited by the small study cohort. The youngest individuals were 13 years old, and vaccines were available from 12 years old at the time of the study. The median age of the vaccinated individuals in the study cohort is similar to the age of individuals who developed SARS-CoV-2-induced chilblains (1, 2, 12). Comparison with the participants in the Pfizer/BioNTech trial on safety is hampered by the difference in populations and designs between the 2 studies. In addition, the level of SARS-CoV-2 antibodies following vaccination was not measured, and it would be interesting to compare this with the level of SARS-CoV-2 antibodies in the general population after vaccination.

In conclusion, COVID-19 vaccination seems to be safe in patients who have previously developed SARS-CoV-2-induced chilblains. No relapse of chilblains occurred, but 6% of the patients developed transient erythromelalgia following vaccination.

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Conflicts of interest: AD reports reimbursement for travel and/or accommodation expenses for attending medical meetings from Sanofi, and personal fees from Sanofi and Leo Pharma, outside of the submitted work.

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