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Tolerance of COVID-19 vaccination in patients with systemic lupus erythematosus: the international VACOLUP study

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131 vaccine candidates have been evaluated for SARS-CoV-2 in more than 380 trials, eventually leading to 20 vaccine approvals[1] and more than 1·8 billion people vaccinated worldwide as of July 1, 2021. There is a paucity of data regarding the safety of COVID-19 vaccines in patients with rheumatic and musculoskeletal diseases[2] such as systemic lupus erythematosus (SLE), because patients with SLE have largely been excluded from vaccine trials.[3-5] Furthermore, the use of mRNA vaccines has raised substantial concerns about the tolerance of these new vaccine technologies in patients with SLE, as toll-like receptor stimulation by nucleic acids might increase the risk of flare. These uncertainties have been shown to be major determinants of reduced vaccination willingness in patients with rheumatic and musculoskeletal diseases.[6] Therefore, the primary objective of the international vaccination against COVID in systemic lupus (VACOLUP) study was to assess the tolerance of COVID-19 vaccines in patients with SLE, including the risk of incident flare, from the patients' perspective.

VACOLUP was a cross-sectional study based on a 43-question web-based survey, which took place between March 22, 2021, and May 17, 2021. The study was approved by the ethics review board of Strasbourg medical faculty (#CE-2020-29) and respondents gave their written informed consent to participate in this research via a dedicated question at the beginning of the online questionnaire. The study targeted patients with a self-reported medically confirmed diagnosis of SLE. The primary outcome was the occurrence of side-effects, including flare. The VACOLUP questionnaire and detailed methods are shown in the appendix (pp 1–2, 7–17).

The study included 696 participants (669 [96%] women and 27 [4%] men) from 30 countries, with a median age of 42 years (IQR 34–51). Detailed patient characteristics are shown in the appendix (p 5). The type of COVID-19 vaccine administered and the occurrence of side-effects after vaccination (as self-reported by patients) are summarised in the table. All patients received at least one dose of vaccine and 343 (49%) patients received a second dose (appendix p 3). The most common vaccines were Pfizer-BioNTech (399 [57%] participants), Sinovac (156 [22%] participants), AstraZeneca (73 [10%] participants), and Moderna (57 [8%] participants; table; appendix p 6).

Side-effects were reported by 316 (45%) patients after the first vaccine dose and by 181 (53%) of 343 patients after the second vaccine dose, with no difference according to gender (308 [46%] of 669 female participants *vs* eight [30%] of 27 male participants; p=0·11), age (median 41 years, IQR 34–50 in patients with side-effects *vs* 43, 35–52 in those without side-effects; p=0·079), or vaccine type (204 [45%] of 456 participants who received mRNA vaccines *vs* 111 [46%] of 239 participants who received vaccines with other modes of action; p=0·69; the participant with unknown vaccine type was excluded). Patients who received both vaccine doses and reported side-effects after the first dose were more likely to report side-effects after the second dose than those who did not (109 [81%] of 135 patients *vs* 72 [35%] of 205 participants; relative risk [RR] 2·30, 95% CI 1·88–2·82; p<0·0001). Occurrence of side-effects by country and vaccine type is shown in the appendix (p 6).

The type and intensity of side-effects reported by patients with SLE are shown in the appendix (p 4). The symptoms were of minor or moderate intensity (ie, without an effect on the ability to do daily tasks) in 2232 (83%) of 2683 cases.

21 (3%) of 696 patients reported a medically confirmed SLE flare (table), typically with predominant musculoskeletal symptoms (19 [90%] patients) and fatigue (18 [86%] patients), after a median of 3 days (IQR 0–29) after COVID-19 vaccination. These flares led to a change in SLE treatment in 15 (71%) of 21 cases and to admission to hospital in four (19%) cases. Having a flare during the past year before vaccination was associated with an increased risk of SLE flare after COVID-19 vaccination (RR 5·52, 95% CI 2·17–14·03; p<0·0001). We found no significant association between side-effects or occurrence of a SLE flare and SLE medications or previous SLE disease manifestations.

To our knowledge, the VACOLUP study is the first large-scale study of tolerance of COVID-19 vaccines in patients with SLE. An important finding of the study

See Online for appendix

	Patients (n=696)
Vaccination	
First dose	696 (100%)
First and second dose	343 (49%)
Vaccine received	
Pfizer-BioNTech	399 (57%)
Sinovac	156 (22%)
AstraZeneca	73 (10%)
Moderna	57 (8%)
Other*	11 (2%)
Side-effects after first vaccine dose	316 (45%)
Timing of onset of side-effects after first dose, days	0 (0–1)
Side-effects after second vaccine dose	181/343 (53%)
Timing of onset of side-effects after second dose, days	0 (0–1)
Consultations or admissions to hospital for side-effects (first and second doses together)	
Medical consultation	81/1039 (8%)
Emergency consultation	14/1039 (1%)
Admission to hospital	5/1039 (<1%)
SLE flare after vaccination	21 (3%)
SLE flare manifestations	
Fever (temperature >38°C or 100·4°F)	10/21 (48%)
Cutaneous (skin) flare (medically confirmed)	12/21 (57%)
Musculoskeletal symptoms (joint, arthritis, arthralgia, or myalgia; medically confirmed)	19/21 (90%)
Pleuritis or pleurisy (medically confirmed)	1/21 (5%)
Pericarditis (medically confirmed)	1/21 (5%)
Renal involvement (medically confirmed)	2/21 (10%)
Neuro-psychiatric manifestations (medically confirmed)	0
Cytopenia (anaemia, thrombocytopenia, or leukocytopenia; medically confirmed)	8/21 (38%)
Low complement (medically confirmed)	5/21 (24%)
Increase in anti-dsDNA antibody titre (medically confirmed)	7/21 (33%)
Fatigue	18/21 (86%)
Consequences of SLE flare	
Change in SLE treatment	15/21 (71%)
Medical consultation	21/21 (100%)
Admission to hospital	4/21 (19%)
COVID-19 after vaccination	0

Data are n (%), median (IQR), or n/N (%). SLE=systemic lupus erythematosus. *Other vaccines were Cansino (one patient), Curevac (one patient), Janssen (five patients), Sinopharm (two patients), Sputnik V (one patient), and unknown (one patient).

Table: **COVID-19 vaccination and consequences**

is that side-effects after COVID-19 vaccination in patients with SLE are common (around 50%) but do not impair daily functioning in most cases. We found no difference in the occurrence of side-effects after receipt of mRNA vaccines compared with vaccines with other modes of action, which is an important and reassuring finding. Finally, the number of medically confirmed flares reported after COVID-19 vaccination was low. The short median time between vaccination and flare onset suggests that it might be difficult to distinguish actual SLE flares from common and expected post-vaccine side-effects, and therefore the 3% figure could be an overestimation of the actual flare rate. Vaccination is recommended[7] for patients with rheumatic and musculoskeletal diseases according to the American College of Rheumatology, irrespective of disease activity and severity, except for those with severe and life-threatening illness (eg, a patient receiving treatment in the intensive care unit for any condition). The main limitation of our study is the self-reported and subjective nature of the outcomes. We tried to mitigate this by asking patients to report only medically confirmed flares. Another limitation is the absence of a control group. However, Furer and colleagues[8] reported that the prevalence of mild adverse events was similar in patients with autoimmune rheumatic and musculoskeletal disease and controls.

In conclusion, the VACOLUP study suggests that COVID-19 vaccination appears well tolerated in patients with SLE, with only a minimal risk of flare, if any, including after the mRNA vaccines. Willingness to get vaccinated against COVID-19 in patients with autoimmune diseases is limited by the fear of side-effects and the paucity of available data.[6] Therefore, disseminating these reassuring data might prove crucial to increasing vaccine coverage in patients with SLE.

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Steroids or intravenous immunoglobulin as first line in MIS-C in LMICs

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SARS-CoV-2 infection in children is associated with lower morbidity and mortality than in adults, with many children experiencing mild symptoms or entirely asymptomatic disease. In April, 2020, a novel condition emerged; this rare, presumed post-COVID-19, immune-mediated hyperinflammatory response was termed paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) by the Royal College Of Paediatrics and Child Health, and multisystem inflammatory syndrome in children (MIS-C) by the US Centers for Disease Control and Prevention and WHO. MIS-C has been associated with variable phenotype and severity, but common features include persistent fever, multiorgan dysfunction, and raised inflammatory markers 2–6 weeks after SARS-CoV-2 infection.

As is the case for acute SARS-CoV-2 infection, health disparities between racial and social groups are also apparent for MIS-C. The condition appears to disproportionately affect children who are from Black, Asian, and other racial and ethnic groups compared with children who are from White racial groups, and children from socially deprived areas.[1,2] As COVID-19 continues to spread across the globe, it is vital that affordable treatment options and protocols suitable for low-income and middle-income countries (LMICs) are made available.

The novelty and heterogeneity of MIS-C presents a considerable challenge in establishing the best treatment strategies. Early in the pandemic, in the absence of available evidence, a consensus of expert opinion was necessary to guide clinicians. As such, a three-phase Delphi process and virtual consensus meeting in the UK summarised recommended pathways for the investigation and management of children with MIS-C.[3] This guideline is applicable in high-income countries, with access to all suggested treatment options and levels of paediatric high dependency and intensive care. In children who require treatment, but are not enrolled in a clinical trial, intravenous immunoglobulin is considered first line, with second doses considered for suboptimal response. High-dose methylprednisolone is recommended as second-line therapy, followed by biologics.[3]

There are several areas of equipoise in the management of MIS-C, including the role of intravenous immunoglobulin and methylprednisolone. A French retrospective cohort study[4] suggested treatment with intravenous immunoglobulin and methylprednisolone was favourable to intravenous immunoglobulin alone, in terms of fever course, left ventricular dysfunction, requirement for haemodynamic support, and duration of paediatric intensive care unit stay. Addition of methylprednisolone to intravenous immunoglobulin was associated with faster recovery of left ventricular ejection fraction in a further single-centre study.[5] A retrospective multicentre US study[6] showed that intravenous immunoglobulin and methylprednisolone was associated with reduced risk of cardiovascular dysfunction and reduced requirement for adjunctive immunomodulatory treatment. The BATS observational cohort study[7] reviewed 614 children from 32 countries, and found no difference in primary