Rheumatology, 2023, **62**, 3838–3848
https://doi.org/10.1093/rheumatology/kead144
Advance access publication 24 March 2023
Original Article

British Society for Rheumatology
RHEUMATOLOGY
OXFORD

Clinical science

Flares in autoimmune rheumatic diseases in the post-COVID-19 vaccination period—a cross-sequential study based on COVAD surveys

Kshitij Jagtap [1], R. Naveen [2], Jessica Day [3,4,5], Parikshit Sen [6], Binit Vaidya [7], Arvind Nune [8], Elena Nikiphorou [9,10], Ai Lyn Tan [11,12], Vishwesh Agarwal [13], Sreoshy Saha [14], Samuel Katsuyuki Shinjo [15], Nelly Ziade [16,17], Mrudula Joshi [18], Tsvetelina Velikova [19], Marcin Milchert [20], Ioannis Parodis [21,22], Abraham Edgar Gracia-Ramos [23], Lorenzo Cavagna [24], Masataka Kuwana [25], Johannes Knitza [26], Ashima Makol [27], Aarat Patel[28], John D. Pauling [29,30], Chris Wincup [31,32], Bhupen Barman [33], Erick Adrian Zamora Tehozol [34], Jorge Rojas Serrano [35], Ignacio García-De La Torre [36], Iris J. Colunga-Pedraza [37], Javier Merayo-Chalico [38], Okwara Celestine Chibuzo [39], Wanruchada Katchamart [40], Phonpen Akawatcharangura Goo[41], Russka Shumnalieva [42], Yi-Ming Chen [43,44], Leonardo Santos Hoff [45], Lina El Kibbi [46], Hussein Halabi [47], Syahrul Sazliyana Shaharir [48], A. T. M. Tanveer Hasan [49], Dzifa Dey [50], Carlos Enrique Toro Gutiérrez [51], Carlo Vinicio Caballero-Uribe [52], James B. Lilleker [53,54], Babur Salim [55], Tamer Gheita [56], Tulika Chatterjee [57], Miguel A. Saavedra [58], Oliver Distler [59], COVAD Study Group[§], Hector Chinoy [53,60,61], Vikas Agarwal [2], Rohit Aggarwal [62,‡], Latika Gupta [53,63,64,*,‡]

[1]Seth Gordhandas Sunderdas Medical College and King Edwards Memorial Hospital, Mumbai, Maharashtra, India
[2]Department of Clinical Immunology and Rheumatology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India
[3]Walter and Eliza Hall Institute of Medical Research, Parkville, VIC, Australia
[4]Department of Medical Biology, University of Melbourne, Parkville, VIC, Australia
[5]Department of Rheumatology, Royal Melbourne Hospital, Parkville, VIC, Australia
[6]Maulana Azad Medical College, New Delhi, Delhi, India
[7]National Center for Rheumatic Diseases (NCRD), Ratopul, Kathmandu, Nepal
[8]Southport and Ormskirk Hospital NHS Trust, Southport, UK
[9]Centre for Rheumatic Diseases, King's College London, London, UK
[10]Rheumatology Department, King's College Hospital, London, UK
[11]NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals Trust, Leeds, UK
[12]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK
[13]Mahatma Gandhi Mission Medical College, Navi Mumbai, Maharashtra, India
[14]Mymensingh Medical College, Mymensingh, Bangladesh
[15]Division of Rheumatology, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, SP, Brazil
[16]Rheumatology Department, Saint-Joseph University, Beirut, Lebanon
[17]Rheumatology Department, Hotel-Dieu de France Hospital, Beirut, Lebanon
[18]Byramjee Jeejeebhoy Government Medical College and Sassoon General Hospitals, Pune, India
[19]Medical Faculty, Sofia University 'St. Kliment Ohridski', Sofia, Bulgaria
[20]Department of Internal Medicine, Rheumatology, Diabetology, Geriatrics and Clinical Immunology, Pomeranian Medical University in Szczecin, Szczecin,Poland
[21]Division of Rheumatology, Department of Medicine Solna, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden
[22]Department of Rheumatology, Faculty of Medicine and Health, Örebro University, Örebro, Sweden
[23]Department of Internal Medicine, General Hospital, National Medical Center, 'La Raza', Instituto Mexicano del Seguro Social, Mexico City, Mexico
[24]Rheumatology Unit, Dipartimento di Medicine Interna e Terapia Medica, Università degli studi di Pavia, Pavia, Lombardy, Italy
[25]Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, Tokyo, Japan
[26]Medizinische Klinik 3—Rheumatologie und Immunologie, Universitätsklinikum Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Deutschland
[27]Division of Rheumatology, Mayo Clinic, Rochester, MN, USA
[28]Bon Secours Rheumatology Center and Division of Pediatric Rheumatology, Department of Pediatrics, University of Virginia School of Medicine, Charlottesville, VA, USA

Received: 6 January 2023. **Accepted:** 19 March 2023

[29]Bristol Medical School Translational Health Sciences, University of Bristol, Bristol, UK
[30]Department of Rheumatology, North Bristol NHS Trust, Bristol, UK
[31]Department of Rheumatology, Division of Medicine, Rayne Institute, University College London, London, UK
[32]Centre for Adolescent Rheumatology Versus Arthritis at UCL, UCLH, GOSH, London, UK
[33]Department of General Medicine, All India Institute of Medical Sciences (AIIMS), Guwahati, India
[34]Rheumatology, Medical Care & Research, Centro Medico Pensiones Hospital, Instituto Mexicano del Seguro Social Delegación Yucatán, Yucatán, Mexcio
[35]Interstitial Lung Disease and Rheumatology Unit, Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico
[36]Departamento de Inmunología y Reumatología, Hospital General de Occidente and Universidad de Guadalajara, Guadalajara, Jalisco, Mexico
[37]Rheumatology, Hospital Universitario Dr Jose Eleuterio Gonzalez, Monterrey, Mexico
[38]Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico
[39]Department of Medicine, University of Nigeria Teaching Hospital, Ituku-Ozalla/University of Nigeria, Enugu Campus, Enugu, Nigeria
[40]Division of Rheumatology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
[41]Department of Medicine, Queen Savang Vadhana Memorial Hospital, Chonburi, Thailand
[42]Department of Rheumatology, Clinic of Rheumatology, University Hospital 'St. Ivan Rilski', Medical University, Sofia, Bulgaria
[43]Division of Allergy, Immunology and Rheumatology, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung City, Taiwan
[44]Department of Medical Research, Taichung Veterans General Hospital, Taichung, Taiwan
[45]School of Medicine, Universidade Potiguar (UnP), Natal, Brazil
[46]Rheumatology Unit, Internal Medicine Department, Specialized Medical Center, Riyadh, Saudi Arabia
[47]Department of Internal Medicine, Section of Rheumatology, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia
[48]Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia
[49]Department of Rheumatology, Enam Medical College & Hospital, Dhaka, Bangladesh
[50]Rheumatology Unit, Department of Medicine and Therapeutics, University of Ghana Medical School, College of Health Sciences, Accra, Ghana
[51]Reference Center for Osteoporosis, Rheumatology and Dermatology, Pontifica Universidad Javeriana Cali, Colombia
[52]Department of Medicine, Hospital Universidad del Norte, Barranquilla, Atlantico, Colombia
[53]Division of Musculoskeletal and Dermatological Sciences, Centre for Musculoskeletal Research, School of Biological Sciences, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, The University of Manchester, Manchester, UK
[54]Manchester Centre for Clinical Neurosciences, Salford Royal NHS Foundation Trust, Salford, UK
[55]Rheumatology Department, Fauji Foundation Hospital, Rawalpindi, Pakistan
[56]Rheumatology Department, Kasr Al Ainy School of Medicine, Cairo University, Cairo, Egypt
[57]Department of Internal Medicine, University of Illinois College of Medicine at Peoria, Peoria, IL, USA
[58]Departamento de Reumatología Hospital de Especialidades Dr. Antonio Fraga Mouret, Centro Médico Nacional La Raza, IMSS, Mexico City, Mexico
[59]Department of Rheumatology, University Hospital Zurich, University of Zurich, Zurich, Switzerland
[60]National Institute for Health Research Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, The University of Manchester, Manchester, UK
[61]Department of Rheumatology, Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust, Salford, UK
[62]Division of Rheumatology and Clinical Immunology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[63]Department of Rheumatology, Royal Wolverhampton Hospitals NHS Trust, Wolverhampton, UK
[64]City Hospital, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK

*Correspondence to: Latika Gupta, Department of Rheumatology, Royal Wolverhampton Hospitals NHS Trust, Wolverhampton, WV10 0QP, UK. Email: drlatikagupta@gmail.com

[‡]R.A. and L.G. are co-senior authors.

[§]See Supplementary Material available at *Rheumatology* online for a complete list of the authors who are part of the COVAD Study Group, as well as their affiliations.

Abstract

Objective: Flares of autoimmune rheumatic diseases (AIRDs) following COVID-19 vaccination are a particular concern in vaccine-hesitant individuals. Therefore, we investigated the incidence, predictors and patterns of flares following vaccination in individuals living with AIRDs, using global COVID-19 Vaccination in Autoimmune Diseases (COVAD) surveys.

Methods: The COVAD surveys were used to extract data on flare demographics, comorbidities, COVID-19 history, and vaccination details for patients with AIRDs. Flares following vaccination were identified as patient-reported (a), increased immunosuppression (b), clinical exacerbations (c) and worsening of PROMIS scores (d). We studied flare characteristics and used regression models to differentiate flares among various AIRDs.

Results: Of 15 165 total responses, the incidence of flares in 3453 patients with AIRDs was 11.3%, 14.8%, 9.5% and 26.7% by definitions a–d, respectively. There was moderate agreement between patient-reported and immunosuppression-defined flares ($K = 0.403$, $P = 0.022$). Arthritis (61.6%) and fatigue (58.8%) were the most commonly reported symptoms. Self-reported flares were associated with higher comorbidities ($P = 0.013$), mental health disorders (MHDs) ($P < 0.001$) and autoimmune disease multimorbidity (AIDm) ($P < 0.001$).
In regression analysis, the presence of AIDm [odds ratio (OR) = 1.4; 95% CI: 1.1, 1.7; $P = 0.003$), or a MHD (OR = 1.7; 95% CI: 1.1, 2.6; $P = 0.007$), or being a Moderna vaccine recipient (OR = 1.5; 95% CI: 1.09, 2.2; $P = 0.014$) were predictors of flares. Use of MMF (OR = 0.5; 95% CI: 0.3, 0.8; $P = 0.009$) and glucocorticoids (OR = 0.6; 95% CI: 0.5, 0.8; $P = 0.003$) were protective.
A higher frequency of patients with AIRDs reported overall active disease post-vaccination compared with before vaccination (OR = 1.3; 95% CI: 1.1, 1.5; $P < 0.001$).

Conclusion: Flares occur in nearly 1 in 10 individuals with AIRDs after COVID vaccination; people with comorbidities (especially AIDm), MHDs and those receiving the Moderna vaccine are particularly vulnerable. Future avenues include exploring flare profiles and optimizing vaccine strategies for this group.

Keywords: COVID-19, vaccination, flares, autoimmunity, rheumatic, vaccination hesitancy

Rheumatology key messages

- Flares were reported by 1 in 10 individuals with autoimmune rheumatic diseases after COVID-19 vaccination.
- Patients with autoimmune disease multimorbidity or mental health disorders, and Moderna vaccine recipients are vulnerable to developing flares.

Introduction

Patients with autoimmune rheumatic diseases (AIRDs) may, in certain circumstances, be predisposed to severe COVID-19 disease due to immune aberrations caused by the disease or the treatment, which makes vaccination particularly essential for this group. Despite emerging literature on vaccine safety in patients with AIRDs [1, 2], hesitancy continues to hinder vaccination [3, 4]. One of the most significant contributors to this hesitancy is the perceived risk of flares of the underlying AIRD [5, 6]. Patients with an AIRD who are on intense immunosuppression qualify for additional COVID-19 vaccine booster doses. There is insufficient data on the impact on flares from vaccine doses, immunosuppressant use, and homologous *vs* heterologous vaccination.

Emergent data on flares in AIRDs are mostly physician-reported and are often in sharp contrast to the level of concern around vaccine safety. Addressing patient concerns regarding vaccination is of prime importance to secure maximum vaccine coverage and care for the vulnerable. Understanding the differences between physician and patient perspectives towards vaccination through analysis of patient-reported data can be particularly invaluable. Given the positive reporting bias in publications on vaccine-induced flares of autoimmune disease, further exploration of this facet of vaccine safety is paramount [7, 8].

The COVID-19 in Autoimmune Rheumatic Diseases (COVAD) study seeks to understand concerns around COVID-19 vaccination in patients with autoimmune diseases and comprises two global patient-reported datasets. The current analysis reports the prevalence and profile of self-reported flares and investigates the disparity between patient-reported and physician-denoted flares. We further attempt to identify any deterioration in physical function, using validated metrics at two end points in a subgroup. Additionally, we explore the predictors of flare in the post-vaccination period and potential future avenues in the care of vulnerable individuals with AIRDs.

Methods

Study design

The COVAD 1 and COVAD 2 studies were conducted in 2021 and 2022, respectively. They are multinational, cross-sectional, patient-self-reported electronic surveys [9, 10]. Informed consent was obtained via a cover letter. Participants were not offered any incentives for completing the survey. Ethical approval was obtained from the Institutional Ethics Committee of the Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow (226014). The Checklist for Reporting Results of the Internet E-Surveys (CHERRIES) was adhered to when reporting the results. The surveys were disseminated throughout 109 countries via 156 collaborators and captured COVID-19 vaccination-related adverse events (AEs) in autoimmune diseases and healthy populations. The first survey captured short-term AEs, whereas the second survey captured long-term AEs following COVID-19 vaccination.

Data collection

We hosted two comprehensive questionnaires compromising 36 COVID-19 and autoimmune disease–related questions on the online platform surveymonkey.com after vetting by international experts, pilot testing and translation into 18 languages. The international COVAD study group circulated both surveys. Along with patient demographics and comorbidities, disease-specific data, including the type of AIRD, duration, clinical symptoms, current medications, and patient-reported outcomes, including PROMIS physical and mental function and quality of life (QoL) scores, were also collected. In addition, we collected data on flares and other AEs following vaccination. Survey methods and the questions have been detailed in the previously published COVAD protocols [9, 10].

Data extraction

Following data collection, the data were extracted on 15 March 2022 and 18 June 2022 from the COVAD 1 and COVAD 2 databases, respectively. Incomplete responses, those vaccinated in mid-2020 (likely trial participants), those with isolated chronic non-rheumatic autoimmune diseases (like type 1 diabetes and multiple sclerosis), healthy respondents, and unvaccinated respondents were excluded from the analysis. Patients with idiopathic inflammatory myopathies (IIMs) were excluded from AIRDs to minimize bias arising out of a disproportionately large presence compared with disease prevalence. Data pertaining to IIMs is being analysed separately (Supplementary Fig. S1, available at *Rheumatology* online).

Definitions

We defined flares in four ways based on different questions in the survey. Further details regarding the definitions are presented in the Supplementary File available at *Rheumatology* online.

a) Flares self-reported (F-SR)—a direct indicator of the patient's perception of flare
b) Flares immunosuppression (F-IS) —an indirect indicator of physician-denoted flare
c) Flares clinical signs directed (F-CS)—the appearance of new clinical signs (rash, muscle weakness, joint pain or

swelling, digital ulcers, shortness of breath, chest pain, dysphagia, fever, fatigue, active kidney disease)

d) Flares by PROMISPF10A worsening (F-PROMIS)—minimal clinically important difference (MCID) 7.9-point worsening of the PROMISPF10a score between the patients who had taken both surveys [11].

We assessed the F-SR, F-IS and F-CS in the COVAD 2 survey respondents. Flares by the last definition (F-PROMIS) were assessed by matching responses from the participants who had taken both surveys.

Homologous immunization is subsequent vaccination by the same vaccine type as the first dose, and heterologous immunization uses a different vaccine type for subsequent doses. Autoimmune disease comorbidities (listed in the Supplementary File available at *Rheumatology* online) included rheumatic and non-rheumatic autoimmune diseases (nRAIDs) coexisting with the primary rheumatic disease.

Statistical analysis

Descriptive data are expressed as frequency (percentage) and median (interquartile range; IQR). Chi-squared (χ^2) and Mann–Whitney U tests were used to compare groups for categorical and continuous variables, respectively. Binary logistic regression by the enter or backward Wald method, adjusting for age, gender, ethnicity, country of residence, type of COVID-19 vaccine received, immunosuppression used before vaccination, and other factors significant in univariate analysis, was used to assess the predictors of flares among AIRDs. Cox regression analysis was used to differentiate flare rates between various AIRDs. Cohen's Kappa (K) was used to check the agreement between various definitions of flares. Statistical analyses were performed using IBM SPSS version 28.

Results

Population demographics

Of the total 15 165 respondents, 9202 provided complete survey responses. Of these, 3453 responses were from patients with AIRDs who had received vaccines. This group formed our study population and was further analysed. The median age was 48 (37–59) years, 84.8% were females, and 1611 (46.7%) were Caucasians. Of the various AIRDs, 1132 (32.7%) had RA, 723 (20.9%) had SLE), 502 (14.5% had multiple AIRDs, 337 (9.7%) had SpA, 191 (5.5%) had SSc, 82 (2.3%) had MCTD or UCTD, and 485 (14.0%) had other AIRDs. Pfizer-BioNTech (43.2%) was the most common vaccine received. Approximately 37% of patients ($n = 1283$) were on glucocorticoids. The COVID-19 antibody status was known in 218 respondents, of which 165 (75.6%) reported antibodies against SARS-CoV-2. Of the 352 matched data points from the two surveys, 191 patients had AIRDs. Active disease was self-reported by 1315 (60.7%) patients prior to the first dose of the vaccine.

Flares of rheumatic disease in AIRD patients following vaccination

Flares were reported by 393/3453 (11.3%), 512/3453 (14.8%), 329/3453 (9.5%) and 51/191 (26.7%) patients by definitions 'F-SR', 'F-IS', 'F-CS', 'F-PROMIS', respectively, with the median time to flare being 57.5 (10.7–188.0) days. The most common symptoms of flare were arthritis (61.6%) and fatigue (58.8%) (Table 1). Notably, 'F-SR' and 'F-CS' were very well aligned (K = 0.898, $P = 0.012$), suggesting patients can identify clinical signs of flare appropriately; 'F-IS' and 'F-SR' showed moderate agreement (K = 0.403, $P = 0.022$), whereas 'F-CS' poorly agreed with 'F-IS' (K = 0.380 $P = 0.023$), suggesting discrepancies between clinical signs and intensity of immunosuppression denoted disease activity awaiting physician action.

Predictors of flare in AIRD patients

AIRD patients with self-reported flare (F-SR) had higher comorbidities (51.9% *vs* 45.3%, $P = 0.013$), mental health disorders (39.9% *vs* 26.6%, $P < 0.001$), and autoimmune disease multimorbidity (AIDm) (36.4% *vs* 26.9%, $P < 0.001$) than those without flare. They also reported lower PROMIS global mental health scores (worse mental health) and higher VAS scores for pain and fatigue (more pain and fatigue) when compared with those without flare (all $P < 0.001$) (Table 2). Subsequent doses of vaccines resulted in reduced flare rates. The flare rates after the second, third and fourth doses were F-SR (16.9%, 10.6% and 7.7%), F-IS (20.6%, 12.6% and 14.9%) and F-CS (14.6%, 8.6% and 6.7%). There was no difference in outcomes between the use of homologous and heterologous vaccines (F-SR: 11.6% *vs* 11.2%, $P = 0.676$).

In the regression analysis, the presence of AIDm (OR = 1.4; 95% CI: 1.1, 1.7; $P = 0.003$) or mental health disorders (OR = 1.7; 95% CI: 1.1, 2.6; $P = 0.007$) and being a recipient of the Moderna vaccine (OR = 1.5; 95% CI: 1.09, 2.2; $P = 0.014$) were associated with patient-reported flare. Multivariate regression identified MMF use (OR = 0.5; 95% CI: 0.3, 0.8; $P = 0.009$) and glucocorticoid use (OR = 0.6; 95% CI: 0.5, 0.8; $P = 0.003$) had a protective effect against flares (Table 3).

A higher frequency of AIRD patients reported active and worsening disease (OR = 2.1, 95% CI: 1.6, 2.6; $P < 0.001$) and overall active disease (OR = 1.3, 95% CI: 1.1, 1.5; $P < 0.001$) post-vaccination compared with before the first vaccine dose (Table 4). The matrix table (Supplementary Table S1, available at *Rheumatology* online) depicts the disease activity status before and after vaccination in patients with AIRDs.

Flare rates and time to flare were comparable among different types of AIRDs, as indicated by a log-rank P-value of 0.418 (Fig. 1). However, patients with MCTD/UCTDs had a higher incidence of F-SR (at 19.5%) compared with patients with other AIRDs. Additionally, recipients of the Moderna vaccine exhibited a higher prevalence of SLE flares [at 8.1 (1.1–58.8)]. Interestingly, individuals of Asian, Caucasian, and Hispanic ethnicities with multiple AIRDs were less likely to experience flares following vaccination, as demonstrated by Supplementary Table S2, available at *Rheumatology* online. This table also presents the disease-specific clinical characteristics of flares of the different AIRDs.

Discussion

In the present study, the incidence of patient-reported flares was 11.3%, with arthritis and fatigue being the most common symptoms. The risk factors for the development of flares were the presence of multiple comorbidities, AIDm and underlying mental health disorders. Moderna recipients flared more often

Table 1. Characteristics of AIRD patients with flare (by four definitions)

Clinical features during a flare	(a) Patient-reported flare ($n=393$), N (%)	(b) Flare by increased need for immunosuppression dose ($n=512$), N (%)	(c) Clinical flare ($n=329$), N (%)	(d) Flare by PROMIS PF-10a 7.9-point worsening ($n=51$), N (%)
Flare incidence (%)	11.3	14.8	9.5	26.7
Rashes	65 (16.5)	41 (8.0)	58 (17.6)	2 (3.9)
Muscle weakness	151 (38.4)	82 (16.0)	129 (39.2)	3 (5.9)
Muscle pain	206 (52.4)	109 (21.3)	177 (53.8)	4 (7.8)
Arthritis in hands	242 (61.6)	137 (26.8)	229 (69.6)	6 (11.8)
Pain in shoulders and hips	179 (45.5)	99 (19.3)	157 (47.7)	4 (7.8)
Arthritis in other joints	211 (53.7)	119 (23.2)	194 (59.0)	4 (7.8)
Raynaud's phenomenon	49 (12.5)	27 (5.3)	41 (12.5)	–
Skin tightening on hands	25 (6.4)	15 (2.9)	25 (7.6)	–
Skin tightening in new areas	14 (3.6)	10 (2.0)	14 (4.3)	–
Finger-tip ulcers	16 (4.1)	9 (1.8)	16 (4.9)	–
Shortness of breath	73 (18.6)	42 (8.2)	66 (20.1)	2 (3.9)
Chest pain	70 (17.8)	37 (7.2)	61 (18.5)	1 (2.0)
Difficulty in swallowing	23 (5.9)	15 (2.9)	19 (5.8)	3 (5.9)
Fever	59 (15.0)	37 (7.2)	56 (17.0)	1 (2.0)
Fatigue	231 (58.8)	128 (25.0)	199 (60.5)	5 (9.8)
Dry eyes	114 (29.0)	55 (10.7)	99 (30.1)	2 (3.9)
Dry mouth	80 (20.4)	45 (8.8)	75 (22.8)	2 (3.9)
Oral/nasal ulcers	43 (10.9)	23 (4.5)	39 (11.9)	1 (2.0)
Severe hair loss	55 (14.0)	37 (7.2)	51 (15.5)	–
Headache	93 (23.7)	55 (10.7)	79 (24.0)	1 (2.0)
Active kidney disease	28 (7.1)	25 (4.9)	28 (8.5)	–
Elevated muscle enzymes	14 (3.6)	11 (2.1)	11 (3.3)	1 (2.0)
Elevated inflammatory markers	115 (29.3)	83 (16.2)	104 (31.6)	2 (3.9)

than other vaccine recipients. The use of MMF and glucocorticoids had a protective effect against flares.

Although the overall incidence of flares was low, it was higher than that found in most other studies. An online survey of 5619 adults with systemic rheumatic diseases reported 4.9% flares requiring treatment modification [12]. A study from the EULAR-COVAX registry had 4.4% physician-reported flares in 5121 patients with rheumatic disorders [13]. A comparison of studies on flares following vaccination, outlined in Table 5 [12, 14–21], depicts varied flare rates across different studies. The preponderance of comorbidities (46%) in the study population combined with a long time-frame for capturing flares is likely responsible for the comparatively higher incidence of flares following vaccination. These observations outline the challenges in identifying the prevalence of flares in AIRDs in the absence of a formal definition of the same, earmarking this as an important agenda for future consensus.

We have reported flares using multiple definitions. Although all the flares were patient-reported, 'F-SR' is a unique patient perspective of disease worsening (11.3%) following vaccination. 'F-IS' refers to flares requiring a change of immunosuppression (14.8%), which indirectly indicates the physician's perspective. Although the incidence of flare did not differ statistically significantly between the flares for the two definitions, there was only moderate Cohen's kappa agreement ($K=0.403$, $P=0.022$) between assessments according to the two definitions. This discrepancy is not unexpected, given physicians' assessment and patients' judgement of disease are often disparate. Conversely, 'F-CS' uses the worsening of clinical symptoms to indicate flares and was aligned strongly with F-SR ($K=0.898$, $P=0.012$). This suggests that the patient-reported data can prove valuable alongside clinically evaluated reports. The ability of patients to identify disease status and clinical signs may be utilized in future studies and virtual clinical trials to supplement purely clinical evaluation–based studies. Immunosuppression-denoted flares appeared less accurate, potentially as this definition was dependent on physician action that may be delayed due to long waiting times for appointments in the post-pandemic health-care systems. Finally, 'F-PROMIS' utilized a relative comparison of disease activity among patients who had completed both COVAD surveys to indicate flare and was high when compared with the other three definitions of flare. Out of the matched 191 patients with AIRDs, 51 (26.7%) reported worsening PROMIS physical function scores, following the second dose of the COVID-19 vaccines. However, the utility of F-PROMIS as an indicator of flare is unclear because of unavailability of a global cut-off or an anchor MCID. Further studies that assess the validity and reliability of PROMIS scores in flare detection among various AIRDs are required. It also emphasizes the need for MCID estimation using various patient-reported indicators to be an agenda for future studies.

The presence of underlying AIDm, both rheumatic and non-rheumatic, was associated with a greater frequency of flares. Although the pathophysiology of various AIRDs is well studied, the exact pathodynamics of flare and remission states remain unknown. The state of remission is no longer considered a restoration to normalcy but rather an active state of balanced homeostasis between pro-inflammatory and anti-inflammatory processes [22]. Therefore, an external trigger like COVID-19 vaccination might disturb the homeostasis in patients with underlying autoimmune disease, resulting in flares. Patients with AIDm may be more susceptible to this phenomenon.

Table 2. Characteristics of AIRD patients with and without flare (patient-reported)

Flare patient-reported	Total AIRDs ($n = 3453$)	AIRD patients with flare following vaccination ($n = 393$) N (%)	AIRD patients without flare following vaccination ($n = 3060$) N (%)	P
Age (mean, SD)	48.3 (14.5)	46.9 (14.1)	48.5 (14.5)	0.055
Age (median, IQR) years	48.0 (37.0–59.0)	48.0 (37.0–57.5)	48.0 (37.0–60.0)	0.055
Gender				
Male	525 (15.2)	57 (14.5)	468 (15.3)	
Female	2928 (84.8)	336 (85.5)	2592 (84.7)	0.681
Ethnicity				0.128
Caucasian	1611 (46.7)	197 (50.1)	1414 (46.2)	
Asian	838 (24.3)	74 (18.8)	764 (25.0)	
Native American	31 (0.9)	3 (0.8)	28 (0.9)	
African American or African origin	175 (5.1)	28 (7.1)	147 (4.8)	
Hispanic	421 (12.2)	46 (11.7)	375 (12.3)	
Mixed	146 (4.2)	16 (4.1)	130 (4.2)	
Others	122 (3.5)	17 (4.3)	105 (3.4)	
I do not want to disclose	109 (3.2)	12 (3.1)	97 (3.2)	
Type of vaccine taken (first and second dose)				0.014
Pfizer	1493 (43.2)	174 (44.3)	1319 (43.1)	
Moderna	248 (7.2)	42 (10.7)	206 (6.7)	
Oxford	967 (28.0)	97 (24.7)	870 (28.4)	
Sinopharm	174 (5.0)	25 (6.4)	149 (4.9)	
Covishield	175 (5.1)	6 (1.5)	169 (5.5)	
Covaxin	25 (0.7)	3 (0.8)	22 (0.7)	
Sputnik	49 (1.4)	7 (1.8)	42 (1.4)	
Johnson & Johnson	29 (0.8)	3 (0.8)	26 (0.8)	
Immunosuppression received prior to vaccination				
MTX	1022 (29.6)	107 (27.2)	915 (29.9)	0.274
MMF	322 (9.3)	301 (9.8)	21 (5.3)	0.004
AZA	268 (7.8)	31 (7.9)	237 (7.7)	0.921
HCQ	1144 (33.1)	113 (28.8)	1031 (33.7)	0.050
SSZ	263 (7.6)	31 (7.9)	232 (7.6)	0.829
LEF	192 (5.6)	23 (5.9)	169 (5.5)	0.788
Oral tacrolimus	27 (0.8)	4 (1.0)	23 (0.8)	0.573
CSA	49 (1.4)	8 (2.0)	41 (1.3)	0.272
IVIGs	20 (0.6)	5 (1.3)	15 (0.5)	0.054
CYC	45 (1.3)	2 (0.5)	43 (1.4)	0.140
Rituximab	152 (4.4)	140 (4.6)	12 (3.1)	0.166
Anti TNF agents	313 (9.1)	33 (8.4)	280 (9.2)	0.624
JAK inhibitors	77 (2.2)	9 (2.3)	68 (2.2)	0.932
Glucocorticoids	–	–	–	0.010
None	2170 (62.8)	276 (70.2)	1894 (61.9)	–
<10 mg a day	971 (28.1)	84 (21.4)	887 (29.0)	–
10–20 mg a day	237 (6.9)	213 (7.0)	24 (6.1)	–
>20 mg a day	75 (2.2)	9 (2.3)	66 (2.2)	–
Comorbidities				
Any comorbidity	**1590 (46.0)**	**204 (51.9)**	**1386 (45.3)**	**0.013**
Asthma	359 (10.4)	57 (14.5)	302 (9.9)	0.005
CKD	182 (5.3)	13 (3.3)	169 (5.5)	0.064
CLD	42 (1.2)	9 (2.3)	33 (1.1)	0.039
COPD	87 (2.5)	11 (2.8)	76 (2.5)	0.707
ILD	127 (3.7)	11 (2.8)	116 (3.8)	0.325
CAD	81 (2.3)	19 (4.8)	62 (2.0)	0.001
DM	183 (5.3)	23 (5.9)	160 (5.2)	0.603
Epilepsy	44 (1.3)	5 (1.3)	39 (1.3)	0.997
Dyslipidaemia	435 (12.6)	54 (13.7)	381 (12.5)	0.468
HIV-AIDS	4 (0.1)	1 (0.3)	3 (0.1)	0.391
Hypertension	669 (19.4)	80 (20.4)	589 (19.2)	0.601
Stroke	31 (0.9)	5 (1.3)	26 (0.8)	0.403
Tuberculosis	36 (1.0)	4 (1.0)	32 (1.0)	0.959
Organ transplant	16 (0.5)	3 (0.8)	13 (0.4)	0.352
Mental health disorders	**972 (28.1)**	**157 (39.9)**	**815 (26.6)**	**<0.001**
Anxiety	614 (17.8)	99 (25.2)	515 (16.8)	<0.001
Bipolar disorder	20 (0.6)	5 (1.3)	15 (0.5)	0.054
Depression	524 (15.2)	84 (21.4)	440 (14.4)	<0.001
Eating disorder	65 (1.9)	13 (3.3)	52 (1.7)	0.027

(continued)

Table 2. (continued)

Flare patient-reported	Total AIRDs ($n = 3453$)	AIRD patients with flare following vaccination ($n = 393$) N (%)	AIRD patients without flare following vaccination ($n = 3060$) N (%)	P
Insomnia	253 (7.3)	42 (10.7)	211 (6.9)	0.007
Schizophrenia	8 (0.2)	2 (0.5)	6 (0.2)	0.225
Substance use disorders	9 (0.3)	2 (0.5)	7 (0.2)	0.305
AID comorbidities				
Yes	**966 (28.0)**	**143 (36.4)**	**823 (26.9)**	**<0.001**
COVID-19 antibody status				
Antibodies present	165/218 (75.6)	27/34 (79.1)	138/184 (75.0)	0.678
PROMIS PF Global 10a (median, IQR)				
Global physical health score	13.0 (12.0–15.0)	13.0 (12.0–15.0)	13.0 (12.0–15.0)	0.148
Global mental health score	**13.0 (10.0–15.0)**	**11.0 (9.0–13.5)**	**13.0 (10.0–15.0)**	**<0.001**
Fatigue VAS	**3.0 (3.0–4.0)**	**3.0 (2.0–4.0)**	**3.0 (3.0–4.0)**	**<0.001**
Pain VAS	**3.0 (1.0–6.0)**	**5.0 (3.0–7.0)**	**3.0 (1.0–5.0)**	**<0.001**

Note, significant figures are presented in bold font. CKD: chronic kidney disease; CLD: chronic liver disease; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; CAD: coronary artery disease; DM: diabetes mellitus; IQR: interquartile range.

Table 3. Factors predicting flares (patient reported) following vaccination among AIRD patients

	Univariate		Multivariable regression		
	OR (95% CI)	P	Beta	OR (95% CI)[a]	P
Age	–	0.055	–0.017	0.98 (0.97, 0.99)	<0.001
Female gender	1.0 (0.7, 1.4)	0.681	0.036	1.0 (0.7, 1.4)	0.821
Asian ethnicity	0.6 (0.5, 0.9)	0.007	–0.206	0.8 (0.6, 1.0)	0.154
Moderna	**2.3 (1.6, 3.3)**	**<0.001**	**0.453**	**1.5 (1.09, 2.2)**	**0.014**
MMF	**0.5 (0.3, 0.8)**	**0.004**	**–0.628**	**0.5 (0.3, 0.8)**	**0.009**
HCQ	0.7 (0.6, 1.0)	0.050	–0.176	0.8 (0.6, 1.0)	0.159
Glucocorticoids	**0.6 (0.5, 0.8)**	**0.001**	**–0.365**	**0.6 (0.5, 0.8)**	**0.003**
Any comorbidity	1.2 (1.05, 1.5)	0.013	0.238	1.2 (0.9, 1.6)	0.058
Asthma	1.5 (1.1, 2.1)	0.005	0.155	1.1 (0.8, 1.6)	0.371
Mental health disorder	**1.6 (1.4, 2.0)**	**<0.001**	**0.562**	**1.7 (1.1, 2.6)**	**0.007**
Anxiety	1.6 (1.3, 3.1)	<0.001	–0.077	0.9 (0.6, 1.3)	0.678
Depression	1.6 (1.2, 2.1)	<0.001	–0.075	0.9 (0.6, 1.3)	0.676
Insomnia	1.6 (1.1, 2.2)	0.007	0.018	1.0 (0.6, 1.5)	0.928
AID comorbidity	**1.5 (1.2, 1.9)**	**<0.001**	**0.348**	**1.4 (1.1, 1.7)**	**0.003**

Note, significant figures are presented in bold font. [a] Binary logistic regression was adjusted for age, gender, ethnicity, vaccine type and other factors significant ($P < 0.05$) or nearing significance ($P < 0.07$) in univariate analysis were used as covariates using enter method.

Table 4. Disease activity status before and after COVID-19 vaccination among AIRD patients (patient self-reported)

Disease activity	Before first dose of vaccine n (%)	After second dose of vaccine n (%)	OR (95% CI)[a]	P
Overall active disease	1315 (60.7)	1407 (65.0)	1.3 (1.1, 1.5)	<0.001
Disease was inactive/remission	670 (30.9)	546 (25.2)	0.7 (0.6, 0.8)	<0.001
Disease was active and worsening	129 (5.9)	256 (11.8)	2.1 (1.6, 2.6)	<0.001
Disease was active but stable	1064 (49.1)	1011 (46.7)	0.9 (0.8, 1.0)	0.106
Disease was active and improving	122 (5.6)	140 (6.4)	1.1 (0.9, 1.4)	0.256
I am not sure	178 (8.2)	210 (9.7)	1.1 (0.9, 1.4)	0.089

Those who responded by multiple responses were excluded from the analysis in this table ($n = 551$ before first vaccine dose, and $n = 913$ after second vaccine dose). [a] OR of disease activity status after second dose of vaccine compared with before first dose of vaccine. AIRD: autoimmune rheumatic disease; OR: odds ratio.

Mental health disorders, prevalent during the pandemic, may also increase the risk of perceived pain and reported autoimmune disease flares. A study by Lu *et al.* suggested a strong bidirectional association between RA and depression, also suggesting the possibility that depression can trigger autoimmune flares due to collateral factors that may not be identified [23]. Indeed, a meta-analysis of 56 studies on RA reported an increase in self-perceived and clinical ratings of disease activity following mental stressors [24]. Patients with mental health disorders may also be more likely to skip medications resulting in disease flares [25].

Notably, the use of immunosuppressants, especially CSs and MMF, was found to be associated with lower post-vaccination flare. Immunosuppression reduces seroconversion

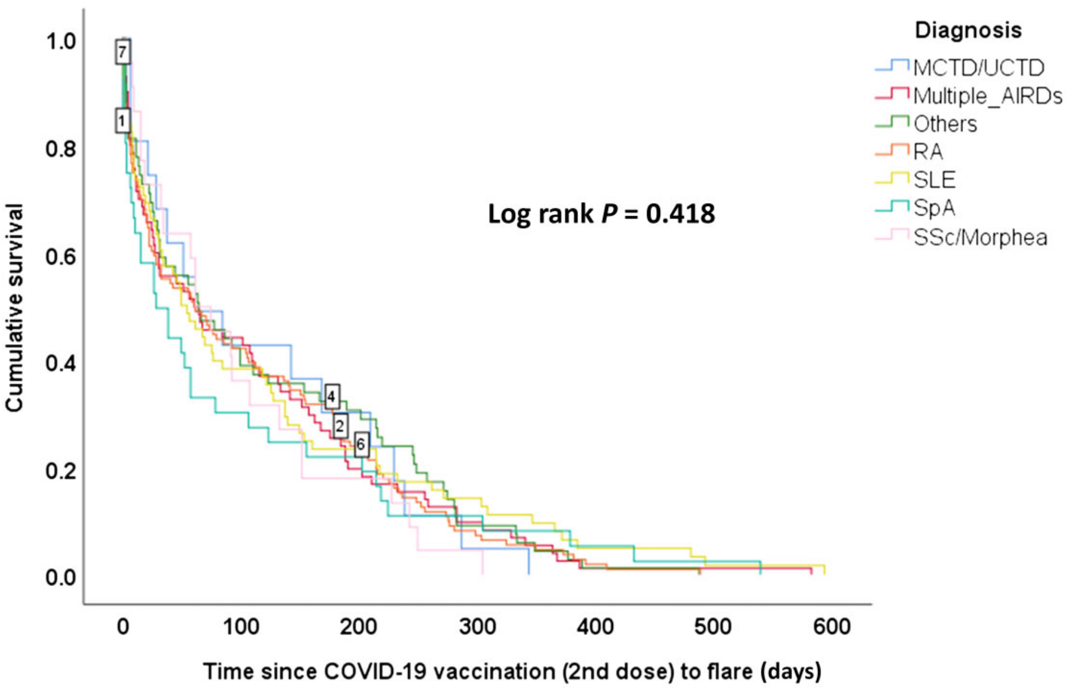

Figure 1. Survival by Cox regression among subtypes of AIRDs. AIRDs: autoimmune rheumatic diseases

rates, rendering the vaccine less immunogenic [7]. There is strong evidence that MMF is responsible for significantly impairing the immune response to multiple vaccines, including Moderna and Pfizer-BioNTech [2, 7, 26]. Glucocorticoids are also speculated to have a dose-dependent reduction in antibody titres [7, 10]. This issue can be addressed by giving a booster dose to achieve adequate antibody titres [27]. Only a small proportion of patients reported their SARS-CoV-2 antibody status in the present study, and this was not found to be predictive for the development of flares.

Heterologous vaccination did not pose any added risk of flares when compared with homologous vaccination in the F-SR group (11.6% *vs* 11.2%, $P = 0.676$). However, subsequent vaccine doses showed reduced flare rates for F-SR, F-IS and F-CS. This could either be due to lower vaccination rates with subsequent doses by those who flared after the first dose, or alternatively due to lower risk of COVID infection–associated flares in those who were better vaccinated. We have identified a high risk of flares in nearly one-third of patients with AIRDs after COVID-19 infection (unpublished data from the COVAD study). Therefore, gauging the risk of flares with successive vaccine doses alongside the minimum number of doses required for adequate seroconversion should be a priority agenda for future studies.

Our study is an invaluable addition to the evidence on flare demographics during the COVID-19 pandemic analysed over a prolonged time-frame. The use of a two-phase survey in our study makes it one of the first online surveys using dual time-frames for collecting data on flares among patients with AIRDs during the COVID pandemic. COVAD-1 and COVAD-2 collect data from distinct time points, making it possible to study short-term and long-term outcomes of COVID-19 vaccination in patients with AIRDs. We studied flares in AIRDs in a large and ethnically diverse population, including a broad range of AIRDs. With a reasonable survey completion rate, the patient-reported structure of this survey studies an unbiased opinion of a largely underrepresented population suffering from AIRDs.

Patient-reported data, being free from external constraints, should be considered complemental to physician-reported data and hence crucial. However, the same patient-reported nature of our study is also responsible for certain limitations, including recall and reporting bias. The data is collected online via patient support groups and social media platforms and could not include patients with severe disabilities and those without access to the internet [20]. It was also beyond the scope of the study to confirm such a large database with the help of medical records like prescriptions and laboratory reports during flares. This shall remain a priority for future prospective studies addressing this research question.

Despite these limitations, our study provides a unique patient perspective of flares following COVID-19 vaccination. A formal definition of flare in AIRDs, particularly using digital tools and patient-reported outcome measures (PROMs) such as PROMIS SF, would be useful for optimizing analysis and interpretation in future studies, including an invaluable addition to virtual clinical trials in the future. Ascertaining the optimum number of vaccine doses based on individualized infection and flare risk in patients with AIRDs remains an important avenue for further exploration.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Table 5. Comparison of flares in AIRDs following COVID-19 vaccination with other studies

Manuscripts	Author	AIRDs	How was flare defined?	Flare incidence	Study population	Data collection
Our Study: Flares in autoimmune rheumatic diseases in the post-COVID-19 vaccination period—a cross-sequential study based on COVAD surveys	Jagtap *et al.*	RA, SLE, SpA, MCTD, SSc, multiple AIRDs	F-SR (a) F-IS (b) F-CS (c) F-PROMIS (d)	11.3% (a) 14.8% (b) 9.5% (c) 26.7% (d)	3453 patients with AIRDs (9202 complete responses)	Online survey
Baseline factors associated with self-reported disease flares following COVID-19 vaccination among adults with systemic rheumatic disease: results from the COVID-19 global rheumatology alliance vaccine survey [12]	Rider *et al.*	SLE, PsA, PMR, Idiopathic inflammatory myopathies (IIMs)	Flare requiring immunomodulation	4.9%	5619 adults with systemic rheumatic disorders	Online survey
Covid-19 vaccination in autoimmune rheumatic diseases: a multicentre survey from southern India [14]	Mohanasundaram *et al.*	RA, SLE, PsA, MCTD, SS, SSc, gout	Patient reported	2.47% ($n = 32$)	2092	Interview-based survey across tertiary healthcare centres in South India
COVID-19 vaccine does not increase the risk of disease flare-ups among patients with autoimmune and immune-mediated diseases [15]	Pinte *et al.*	RA, SLE, SS, PsA	Flare requiring immunomodulation or hospitalization or worsened by clinical features	6% (25/416)	623	Online survey
COVID-19 vaccine hesitancy in patients with systemic autoimmune rheumatic disease: an interview-based survey [16]	Gaur *et al.*	RA, SpA, SLE	Flare requiring immunomodulation	Negligible (1/280)	382	Interview-based survey
Two-dose COVID-19 vaccination and possible arthritis flare among patients with rheumatoid arthritis in Hong Kong [17]	Xue Li *et al.*	RA	Flares requiring immunomodulation/ hospitalization	BNT162b2 recipients: 35/653 (5%) CoronaVac recipients: 41/671 (6%)	5493 patients with RA	Population-based electronic medical record (EMR)
Early experience of COVID-19 vaccination in adults with systemic rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance Vaccine Survey [18]	Sattui *et al.*	RA, IIM, SS, SLE, SpA	Patient reported (a) Flare requiring immunomodulation (b)	13.4% (a) 4.6% (b)	2860 with rheumatic disorders	Online survey
Safety of vaccination against SARS-CoV-2 in people with rheumatic and musculoskeletal diseases: results from the EULAR Coronavirus Vaccine (COVAX) physician-reported registry [19]	Machado *et al.*	RA, PsA, SpA, SLE, SSc, vasculitis, non-inflammatory rheumatic disorders	Patient reported (a) Patients requiring immunomodulation (b)	4.4% (a) 1.5% (b)	5121 with rheumatic disorders	Physician-reported registry
Side effects and flares risk after SARS-CoV-2 vaccination in patients with systemic lupus erythematosus [20]	Zavala-Flores *et al.*	SLE	Flares following first dose (a) Flares following second dose (b)	9% (9/100) (a) 20% (18/90) (b)	100	Hospital visits
Disease flare and reactogenicity in patients with rheumatic and musculoskeletal diseases following two-dose SARS-CoV-2 messenger RNA vaccination [21]	Connolly *et al.*	Inflammatory arthritis, SLE, overlap CTDs	Flares requiring immunomodulation	11%	1377 patients with rheumatic disorders	Online survey

COVAD: COVID-19 Vaccination in Autoimmune Diseases; F-SR: self-reported flares; F-IS: flares defined by immunosuppression; F-CS: flares defined by clinical signs; F-PROMIS: flares defined by PROMISPF10A worsening.

Contribution statement

L.G., K.J. and N.R. were responsible for conceptualization of the study. All authors were involved in data curation. N.R. undertook the formal analysis. L.G., K.J., N.R. and P.S. undertook investigation. L.G., V.A., N.R. and K.J. were responsible for designing the methodology. L.G. was responsible for the software selection and use. V.A., R.A., J.B.L. and H.C. undertook validation. R.A., V.A. and L.G. contributed visualization. K.J., N.R., P.S. and L.G. wrote the original draft of the manuscript. All authors undertook the reviewing and editing of the manuscript.

Funding

No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript. H.C. was supported by the National Institution for Health Research Manchester Biomedical Research Centre Funding Scheme.

Disclosure statement: A.L.T. has received honoraria for advisory boards and for speaking from Abbvie, Gilead, Janssen, Lilly, Novartis, Pfizer, and UCB. E.N. has received speaker honoraria/participated in advisory boards for Celltrion, Pfizer, Sanofi, Gilead, Galapagos, AbbVie, and Lilly, and holds research grants from Pfizer and Lilly. M.K. has received speaker honoraria/participated in advisory boards for Abbvie, Asahi-Kasei, Astellas, AstraZeneca, Boehringer-Ingelheim, Chugai, Corbus, Eisai, GSK, Horizon, Kissei, BML, Mochida, Nippon Shinyaku, Ono Pharmaceuticals, and Tanabe-Mitsubishi. H.C. has received grant support from Eli Lilly and UCB, consulting fees from Novartis, Eli Lilly, Orphazyme, and Astra Zeneca, and speaker fees from UCB, and Biogen. I.P. has received research funding and/or honoraria from Amgen, AstraZeneca, Aurinia Pharmaceuticals, Elli Lilly and Company, Gilead Sciences, GlaxoSmithKline, Janssen Pharmaceuticals, Novartis and F. Hoffmann-La Roche AG. J.B.L. has received speaker honoraria/participated in advisory boards for Sanofi Genzyme, Roche, and Biogen; none are related to this manuscript. J.D.P. has undertaken consultancy work and/or received speaker honoraria from AstraZeneca, Boehringer Ingelgheim, Sojournix Pharma, Permeatus Inc, Janssen and IsoMab Pharmacueticals. J.D. has received research funding from CSL Limited. N.Z. has received speaker fees, advisory board fees, and research grants from Pfizer, Roche, Abbvie, Eli Lilly, NewBridge, Sanofi-Aventis, Boehringer Ingelheim, Janssen, and Pierre Fabre; none are related to this manuscript. O.D. has/had consultancy relationship with and/or has received research funding from and/or has served as a speaker for the following companies in the area of potential treatments for systemic sclerosis and its complications in the last three calendar years: 4P-Pharma, Abbvie, Acceleron, Alcimed, Altavant, Amgen, AnaMar, Arxx, AstraZeneca, Baecon, Blade, Bayer, Boehringer Ingelheim, Corbus, CSL Behring, Galderma, Galapagos, Glenmark, Gossamer, iQvia, Horizon, Inventiva, Janssen, Kymera, Lupin, Medscape, Merck, Miltenyi Biotec, Mitsubishi Tanabe, Novartis, Prometheus, Redxpharma, Roivant, Sanofi and Topadur; O.D. has a patent issued 'mir-29 for the treatment of systemic sclerosis' (US8247389, EP2331143). R.A. has a consultancy relationship with and/or has received research funding from the following companies: Bristol Myers-Squibb, Pfizer, Genentech, Octapharma, CSL Behring, Mallinckrodt, AstraZeneca, Corbus, Kezar, Abbvie, Janssen, Kyverna Alexion, Argenx, Q32, EMD-Serono, Boehringer Ingelheim, Roivant, Merck, Galapagos, Actigraph, Scipher, Horizon Therepeutics, Teva, Beigene, ANI Pharmaceuticals, Biogen, Nuvig, Capella Bioscience, and CabalettaBio. T.V. has received speaker honoraria from Pfizer and AstraZeneca. The rest of the authors have declared no conflicts of interest. The views expressed in this publication are those of the authors and not necessarily those of the NHS, National Institute for Health Research, or Department of Health.

Acknowledgements

The authors are grateful to all respondents for completing the questionnaire. The authors also thank the Myositis Association, Myositis India, Myositis UK, Myositis Support and Understanding, the Myositis Global Network, Deutsche Gesellschaft für Muskelkranke e. V. (DGM), the Dutch and Swedish Myositis patient support groups, Cure JM, Cure IBM, the Sjögren's India Foundation, Patients Engage, Scleroderma India, Lupus UK, Lupus Sweden, the Emirates Arthritis Foundation, EULAR PARE, the ArLAR research group, the AAAA patient group, the Myositis Association of Australia, the APLAR myositis special interest group, the Thai Rheumatism association, PANLAR, AFLAR NRAS, the Anti-Synthetase Syndrome support group, and various other patient support groups and organizations for their contribution to the dissemination of this survey. Finally, the authors wish to thank all members of the COVAD study group for their invaluable role in the data collection. The COVAD study group authors are Zoltán Griger, Sinan Kardes, Laura Andreoli, Daniele Lini, Karen Schreiber, Melinda Nagy Vince, Yogesh Preet Singh, Rajiv Ranjan, Avinash Jain, Sapan C Pandya, Rakesh Kumar Pilania, Aman Sharma, Manesh Manoj M, Vikas Gupta, Chengappa G Kavadichanda, Pradeepta Sekhar Patro, Sajal Ajmani, Sanat Phatak, Rudra Prosad Goswami, Abhra Chandra Chowdhury, Ashish Jacob Mathew, Padnamabha Shenoy, Ajay Asranna, Keerthi Talari Bommakanti, Anuj Shukla, Arunkumar R. Pande, Kunal Chandwar, Akanksha Ghodke, Hiya Boro, Zoha Zahid Fazal, Döndü Üsküdar Cansu, Reşit Yıldırım, Armen Yuri Gasparyan, Nicoletta Del Papa, Gianluca Sambataro, Atzeni Fabiola, Marcello Govoni, Simone Parisi, Elena Bartoloni Bocci, Gian Domenico Sebastiani, Enrico Fusaro, Marco Sebastiani, Luca Quartuccio, Franco Franceschini, Pier Paolo Sainaghi, Giovanni Orsolini, Rossella De Angelis, Maria Giovanna Danielli, Vincenzo Venerito, Silvia Grignaschi, Alessandro Giollo, Alessia Alluno, Florenzo Ioannone, Marco Fornaro, Lisa S Traboco, Suryo Anggoro Kusumo Wibowo, Jesús Loarce-Martos, Sergio Prieto-González, Raquel Aranega Gonzalez, Akira Yoshida, Ran Nakashima, Shinji Sato, Naoki Kimura, Yuko Kaneko, Takahisa Gono, Stylianos Tomaras, Fabian Nikolai Proft, Marie-Therese Holzer, Margarita Aleksandrovna Gromova, Or Aharonov, Zoltán Griger, Ihsane Hmamouchi, Imane El bouchti, Zineb Baba, Margherita Giannini, François Maurier, Julien Campagne, Alain Meyer, Daman Langguth, Vidya Limaye, Merrilee Needham, Nilesh Srivastav, Marie Hudson, Océane Landon-Cardinal, Wilmer Gerardo Rojas Zuleta, Álvaro Arbeláez, Javier Cajas, José António Pereira Silva, João Eurico Fonseca, Olena Zimba, Doskaliuk Bohdana, Uyi Ima-

Edomwonyi, Ibukunoluwa Dedeke, Emorinken Airenakho, Nwankwo Henry Madu, Abubakar Yerima, Hakeem Olaosebikan, Becky A., Oruma Devi Koussougbo, Elisa Palalane, Ho So, Manuel Francisco Ugarte-Gil, Lyn Chinchay, José Proaño Bernaola, Victorio Pimentel, Hanan Mohammed Fathi, Reem Hamdy A Mohammed, Ghita Harifi, Yurilís Fuentes-Silva, Karoll Cabriza, Jonathan Losanto, Nelly Colaman, Antonio Cachafeiro-Vilar, Generoso Guerra Bautista, Enrique Julio Giraldo Ho, Lilith Stange Nunez, Cristian Vergara M, Jossiell Then Báez, Hugo Alonzo, Carlos Benito Santiago Pastelin, Rodrigo García Salinas, Alejandro Quiñónez Obiols, Nilmo Chávez, Andrea Bran Ordóñez, Sandra Argueta, Gil Alberto Reyes Llerena, Radames Sierra-Zorita, Dina Arrieta, Eduardo Romero Hidalgo, Ricardo Saenz, Idania Escalante M, Wendy Calapaqui, Ivonne Quezada, and Gabriela Arredondo.

References

1. Boekel L, Kummer LY, van Dam KPJ *et al.* Adverse events after first COVID-19 vaccination in patients with autoimmune diseases. Lancet Rheumatol 2021;3:e542–5.
2. Furer V, Eviatar T, Zisman D *et al.* Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. Ann Rheum Dis 2021;80:1330–8.
3. Ko T, Dendle C, Woolley I, Morand E, Antony A. SARS-COV-2 vaccine acceptance in patients with rheumatic diseases: a cross-sectional study. Hum Vaccin Immunother 2021;17:4048–56.
4. Tharwat S, Abdelsalam HA, Abdelsalam A, Nassar MK. COVID-19 vaccination intention and vaccine hesitancy among patients with autoimmune and autoinflammatory rheumatological diseases: a survey. Int J Clin Pract 2022;2022:e5931506.
5. Naveen R, Joshi M, Sen P *et al.* Vaccine hesitancy among patients with idiopathic inflammatory myopathies and rheumatic diseases in 2021–2022: a comparative analysis of COVID-19 vaccination in autoimmune diseases surveys. ACR Meeting Abstracts. https://acrabstracts.org/abstract/vaccine-hesitancy-among-patients-with-idiopathic-inflammatory-myopathies-and-rheumatic-diseases-in-2021-2022-a-comparative-analysis-of-covid-19-vaccination-in-autoimmune-diseases-surveys/ (5 December 2022, date last accessed).
6. Sen P, Lilleker JB, Agarwal V *et al.* Vaccine hesitancy in patients with autoimmune diseases: Data from the coronavirus disease-2019 vaccination in autoimmune diseases study. Indian J Rheumatol 2022;17:188–91.
7. Paik JJ, Sparks JA, Kim AHJ. Immunogenicity, breakthrough infection, and underlying disease flare after SARS-CoV-2 vaccination among individuals with systemic autoimmune rheumatic diseases. Curr Opin Pharmacol 2022;65:102243.
8. Terracina KA, Tan FK. Flare of rheumatoid arthritis after COVID-19 vaccination. Lancet Rheumatol 2021;3:e469–70.
9. Sen P, Gupta L, Lilleker JB *et al.*; COVAD Study Group. COVID-19 vaccination in autoimmune disease (COVAD) survey protocol. Rheumatol Int 2022;42:23–9.
10. Fazal ZZ, Sen P, Joshi M *et al.*; COVAD Study Group. COVAD survey 2 long-term outcomes: unmet need and protocol. Rheumatol Int 2022;42:2151–8.
11. Gollgher EC, Pouchot J, Brant R *et al.* Minimal clinically important difference for 7 measures of fatigue in patients with systemic lupus erythematosus. J Rheumatol 2008;35:635–42.
12. Rider LG, Parks CG, Wilkerson J *et al.*; COVID-19 Global Rheumatology Alliance Vaccine Survey Group. Baseline factors associated with self-reported disease flares following COVID-19 vaccination among adults with systemic rheumatic disease: results from the COVID-19 global rheumatology alliance vaccine survey. Rheumatology (Oxford) 2022;61:SI143–50.
13. Machado PM, Lawson-Tovey S, Strangfeld A *et al.* Safety of vaccination against SARS-CoV-2 in people with rheumatic and musculoskeletal diseases: results from the EULAR Coronavirus Vaccine (COVAX) physician-reported registry. Ann Rheum Dis 2022;81:695–709.
14. Bozzalla-Cassione E, Grignaschi S, Xoxi B *et al.* Insights into the concept of rheumatoid arthritis flare. Front Med 2022;9:852220.
15. Lu MC, Guo HR, Lin MC *et al.* Bidirectional associations between rheumatoid arthritis and depression: a nationwide longitudinal study. Sci Rep 2016;6:20647.
16. Geenen R, Van Middendorp H, Bijlsma JWJ. The impact of stressors on health status and hypothalamic–pituitary–adrenal axis and autonomic nervous system responsiveness in rheumatoid arthritis. Ann N Y Acad Sci 2006;1069:77–97.
17. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med 2000;160:2101–7.
18. De Santis M, Motta F, Isailovic N *et al.* Dose-dependent impairment of the immune response to the moderna-1273 mRNA vaccine by mycophenolate mofetil in patients with rheumatic and autoimmune liver diseases. Vaccines (Basel) 2022;10:801.
19. Lee ARYB, Wong SY, Tay SH. Booster COVID-19 vaccines for immune-mediated inflammatory disease patients: a systematic review and meta-analysis of efficacy and safety. Vaccines (Basel) 2022;10:668.
20. Philp F, Faux-Nightingale A, Bateman J *et al.* Observational cross-sectional study of the association of poor broadband provision with demographic and health outcomes: the Wolverhampton Digital ENablement (WODEN) programme. BMJ Open 2022;12:e065709.
21. Mohanasundaram K, Santhanam S, Natarajan R *et al.* Covid-19 vaccination in autoimmune rheumatic diseases: a multi-center survey from southern India. Int J Rheum Dis 2022;25:1046–52.
22. Pinte L, Negoi F, Ionescu GD *et al.* COVID-19 vaccine does not increase the risk of disease flare-ups among patients with autoimmune and immune-mediated diseases. J Pers Med 2021;11:1283.
23. Gaur P, Agrawat H, Shukla A. COVID-19 vaccine hesitancy in patients with systemic autoimmune rheumatic disease: an interview-based survey. Rheumatol Int 2021;41:1601–5.
24. Li X, Tong X, Yeung WWY *et al.* Two-dose COVID-19 vaccination and possible arthritis flare among patients with rheumatoid arthritis in Hong Kong. Ann Rheum Dis 2022;81:564–8.
25. Sattui SE, Liew JW, Kennedy K *et al.* Early experience of COVID-19 vaccination in adults with systemic rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance Vaccine Survey. RMD Open 2021;7:e001814.
26. Zavala-Flores E, Salcedo-Matienzo J, Quiroz-Alva A, Berrocal-Kasay A. Side effects and flares risk after SARS-CoV-2 vaccination in patients with systemic lupus erythematosus. Clin Rheumatol 2022;41:1349–57.
27. Connolly CM, Ruddy JA, Boyarsky BJ *et al.* Disease flare and reactogenicity in patients with rheumatic and musculoskeletal diseases following two-dose SARS-CoV-2 messenger RNA vaccination. Arthritis Rheumatol 2022;74:28–32.