EPIDEMIOLOGICAL SCIENCE

Safety of vaccination against SARS-CoV-2 in people with rheumatic and musculoskeletal diseases: results from the EULAR Coronavirus Vaccine (COVAX) physician-reported registry

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ABSTRACT

Objectives To describe the safety of vaccines against SARS-CoV-2 in people with inflammatory/autoimmune rheumatic and musculoskeletal disease (I-RMD).

Methods Physician-reported registry of I-RMD and non-inflammatory RMD (NI-RMDs) patients vaccinated against SARS-CoV-2. From 5 February 2021 to 27 July 2021, we collected data on demographics, vaccination, RMD diagnosis, disease activity, immunomodulatory/immunosuppressive treatments, flares, adverse events (AEs) and SARS-CoV-2 breakthrough infections. Data were analysed descriptively.

Results The study included 5121 participants from 30 countries, 90% with I-RMDs (n=4604, 68% female, mean age 60.5 years) and 10% with NI-RMDs (n=517, 77% female, mean age 71.4). Inflammatory joint diseases (58%), connective tissue diseases (18%) and vasculitis (12%) were the most frequent diagnostic groups; 54% received conventional synthetic disease-modifying antirheumatic drugs (DMARDs), 42% biological DMARDs and 35% immunosuppressants. Most patients received the Pfizer/BioNTech vaccine (70%), 17% AstraZeneca/Oxford and 8% Moderna. In fully vaccinated cases, breakthrough infections were reported in 0.7% of I-RMD patients and 1.1% of NI-RMD patients. I-RMD flares were reported in 4.4% of cases (0.6% severe), 1.5% resulting in medication changes. AEs were reported in 37% of cases (37% I-RMD, 40% NI-RMD), serious AEs in 0.5% (0.4% I-RMD, 1.9% NI-RMD).

Conclusion The safety profiles of SARS-CoV-2 vaccines in patients with I-RMD was reassuring and comparable with patients with NI-RMDs. The majority of patients tolerated their vaccination well with rare reports of I-RMD flare and very rare reports of serious AEs. These findings should provide reassurance to rheumatologists and vaccine recipients and promote confidence in SARS-CoV-2 vaccine safety in I-RMD patients.

Key messages

What is already known about this subject?

- People with inflammatory/autoimmune rheumatic and musculoskeletal diseases (I-RMDs) were excluded from SARS-CoV-2 vaccine clinical development programmes; therefore, concerns regarding the safety and effectiveness of SARS-CoV-2 vaccines in this population still exist.
- Previous studies in people with I-RMDs were small albeit reassuring in terms of the incidence of I-RMD flares and adverse events.

INTRODUCTION

The WHO declared the SARS-CoV-2 outbreak a Public Health Emergency of International Concern on 30 January 2020 and a pandemic on 11 March 2020. The COVID-19 pandemic has led to a dramatic loss of human life and an unprecedented challenge to public health and healthcare systems worldwide.[1]

Since the publication of the genome sequence of SARS-CoV-2 on 11 January 2020, the development of vaccines against SARS-CoV-2 accelerated at an extraordinary pace; in December 2020, two vaccines using mRNA technology (Pfizer/BioNTech and Moderna) and one vaccine using a non-replicating adenoviral vector expressing the spike protein (AstraZeneca/Oxford) were authorised for use by several national and international drug regulatory bodies.[1] According to the WHO, on 17 August 2021, there were 112 candidate vaccines in human clinical trial phases and 183 candidates in preclinical development worldwide.[2]

Vaccines are a key pillar of public health and the WHO estimates that vaccine immunisation currently prevents 4–5 million deaths every year.[3]

Key messages

What does this study add?

- In this large international registry of patients with I-RMDs vaccinated against SARS-CoV-2, the overwhelming majority of patients tolerated their vaccination well with rare reports of I-RMD flare (4.4%, 0.6% severe, 1.5% requiring medication changes) and very rare reports of serious adverse events (AEs) (0.4%) and breakthrough infections, namely in fully vaccinated patients (0.7%).
- The AE profile was similar to the one observed in patients with non-inflammatory RMDs (and the general population). They were mainly non-serious transient local and systemic reactions.

How might this impact on clinical practice or future developments?

- These findings will support discussions with patients regarding the safety profile and benefit/risk ratio of vaccination against SARS-CoV-2 and the development of recommendations by competent organisations.
- These findings should provide reassurance to rheumatologists, other health professionals and vaccine recipients and promote confidence in SARS-CoV-2 vaccine safety in I-RMD patients.

Many more lives are expected to be saved with immunisation against SARS-CoV-2, which has been shown to be highly effective.[4–8] However, vaccination also raises questions, especially for patients with inflammatory/autoimmune rheumatic and musculoskeletal diseases (I-RMDs) and/or treated with drugs that may influence the functional competence of their immune system.

Patients with immune-mediated inflammatory diseases (including I-RMDs) were excluded from SARS-CoV-2 vaccine clinical development programmes; therefore, questions regarding the safety, effectiveness and potential measures that may increase the safety and effectiveness of vaccination against SARS-CoV-2 are unanswered.[9 10] Lack of data has led to some contradictory advice from rheumatology organisations and healthcare professionals regarding some of these vaccination aspects.[11 12] Further data will contribute to more informed decisions by patients and healthcare professionals and more robust and homogeneous evidence-based recommendations from relevant organisations. Our aim was therefore to describe the safety of vaccines against SARS-CoV-2 in people with I-RMDs.

Of note, adverse events reported in these manuscript should be considered adverse events following immunisation (AEFI), as defined by the WHO that is, 'any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine'. Investigating causality of AEFIs, particularly those that are more serious, is a much more challenging and complex process that should take the consistence, strength, specificity, temporal relation and biological plausibility of the association into account.

METHODS

Data source

The European Alliance of Associations for Rheumatology (EULAR) Coronavirus Vaccine (COVAX) physician-reported registry was launched on 5 February 2021. Data are entered voluntarily by rheumatologists or other members of the clinical rheumatology team; patients are eligible for inclusion if they have a pre-existing I-RMD or non-inflammatory rheumatic and musculoskeletal disease (NI-RMD) and have received one or more doses of any vaccine against SARS-CoV-2. Data are entered directly into an online data entry system or transferred from national registries (for Portugal). Patients with NI-RMDs are included as a control group.

Providers were asked to report as many cases as possible of patients with rheumatic and musculoskeletal disease (RMDs) vaccinated against SARS-CoV-2, with or without adverse events. Cases could be collected in outpatient, day care or inpatient settings, with the number of reported cases per session varying depending on feasibility. When reporting only a subset of patients from, for example, a full clinic list, providers were asked to select cases randomly, in order to avoid selection bias. Furthermore, the time from vaccination to the reporting of the case/outcome was allowed to vary between individuals, and providers were also asked not to report adverse events that, in the opinion of the reporter, were definitely not related with the vaccine administration (eg, death as a consequence of road traffic accident).

Data are collected using REDCap, a secure web application for building and managing online surveys and databases.[13 14] The survey (available at https://www.eular.org/eular_covax_registry.cfm) was developed by a EULAR COVID-19 Task Force of representatives of its constituents, patients and health professionals in rheumatology and rheumatologists. Input and support was also received from the European Reference Network (ERN) on Rare and Complex Connective Tissue and Musculoskeletal Diseases (ERN ReCONNET) and the European Reference Network on Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases Network (ERN RITA), two virtual networks involving healthcare providers across Europe, part of the EU-supported ERN initiative.

Given the registry collects anonymous non-interventional data, the UK Health Research Authority (HRA) does not class the registry as a research study (in line with the HRA decision tool), and patient consent is not required. By submitting cases, providers accept the privacy notice available on the data collection website.

Data collected

The following information is collected: patients' age (years), sex at birth, country of residence, COVID-19 vaccine received, number of doses and dates, diagnosis of COVID-19 before or after vaccination, primary (and secondary) RMD diagnoses, physician global assessment of disease activity (only applicable to I-RMDs and categorised as remission/inactive disease, low, moderate or severe/high disease activity), exposure to immunomodulatory/immunosuppressive treatments at the time of vaccination,[9] I-RMD flare following vaccination and other probably/possibly vaccine-related adverse events (AEs), including AEs of special interest. SARS-CoV-2 infections stratified by vaccination status were defined as per US Centers for Disease Control and Prevention definitions[15]: (1) infection in 'partially vaccinated' cases if occurring ≥14 days after dose one to <14 days after dose two, and (2) infection in 'fully vaccinated' cases if occurring ≥14 days after dose two or after a single-dose vaccine.

Immunomodulatory/immunosuppressive treatments

Exposure to the following immunomodulatory/immunosuppressive treatments[16] at the time of COVID-19 vaccination is collected:

1. Conventional synthetic (cs) disease-modifying antirheumatic drugs (DMARDs), namely antimalarials

(hydroxychloroquine and chloroquine), leflunomide, methotrexate and sulfasalazine.
2. Biological (b) DMARDs, namely abatacept, belimumab, rituximab, interleukin (IL)-1 inhibitors (including anakinra, canakinumab and rilonacept), IL-6 inhibitors (including tocilizumab, sarilumab), IL-12/23 inhibitors (ustekinumab), IL-23 inhibitors (including guselkumab, risankizumab and tildrakizumab), IL-17 inhibitors (including secukinumab, ixekizumab and brodalumab) and tumour necrosis factor (TNF) inhibitors (including adalimumab, certolizumab, etanercept, golimumab, infliximab and biosimilars).
3. Targeted synthetic (ts) DMARDs, namely apremilast and JAK inhibitors (including tofacitinib, baricitinib and upadacitinib).
4. Immunosuppressants: glucocorticoids (GCs), azathioprine/6-mercaptopurine, cyclophosphamide, ciclosporin, mycophenolate mofetil and tacrolimus.
5. Intravenous immunoglobulin.

For each medication, information about changes in the original therapeutic regimen before or after COVID-19 vaccination (including stopping/holding/reducing the medication) is also collected.

Flares

For patients with I-RMDs, information about flares is collected, namely: (1) type of flare (fever, weight loss, increase in fatigue, increase in dryness, enlarged lymph nodes, arthralgia, arthritis flare, cutaneous, pulmonary, renal, neurological, muscular, cardiac, gastrointestinal or haematological flare or other type of flare); (2) severity of flare (mild/minor, moderate, severe/major without hospitalisation and severe/major with hospitalisation); (3) information about changes in medication (including dosage increase) due to the flare; and (4) period of time between vaccination and the flare.

Adverse events

Two main types of AEs are collected:
1. Early AEs within 7 days from vaccination (reactogenicity): pain, redness or swelling at the site of injection, generalised muscle or joint pain, headache, fever, chills, fatigue, vomiting and diarrhoea.
2. AEs of special interest: collected based on organ/system affected, with the possibility to add free-text descriptors.

Information about the period of time between vaccination and the AE, degree of confidence in the relationship between the AE and the COVID-19 vaccine, outcome (ongoing/continuing, recovered/resolved without sequelae, recovered/resolved with sequelae, death and unknown) and if the AE was serious or not is also collected.

Serious AEs (SAEs) are further categorised into six possible groups: resulting in an important medical event, resulting in hospitalisation or prolongation of existing hospitalisation (hospitalisation being defined as at least 24 hours in a hospital or an overnight stay), life-threatening event, resulting in persistent or significant disability/incapacity, resulting in death or resulting in congenital anomaly/birth defect.

Statistical analysis

Descriptive statistics, including means and SD, frequencies and proportions, are used to describe the data. Data are presented separately for patients with I-RMD and NI-RMD. Crystal arthropathies were included in the NI-RMD group as these patients are not usually treated with immunomodulatory/immunosuppressive drugs. Missing data were treated as missing.

RESULTS

Demographics

Between 5 February 2021 and 27 July 2021, 5121 cases were submitted to the EULAR COVAX registry (table 1). Seventy per cent of these cases were female, the mean age was 61.6 (SD 15.2), and over half of the cases were over the age of 60 years (56%). Cases were submitted from 30 countries, the majority from France (40%), Italy (16%) and Portugal (14%). Providers were from diverse rheumatology practices, including academic and non-academic centres, and a minority of private practices. The I-RMD group made up 90% of all cases (n=4604), with a mean age of 60.5 (SD 15.1) and 68% of this group were female. The NI-RMD group (10%, n=517) had a higher percentage of female cases (77%) and a higher mean age (71.4, SD 12.5), with 80% of the group having an age over 60 years. Mean time between first vaccine dose and case reporting was 66 days (SD 40), 66 days (SD 40) in the I-RMD group and 64 days (SD 40) in the NI-RMD group.

RMD data

Over half of the cohort had an inflammatory joint disease as their primary RMD diagnosis (58%), 18% had a connective tissue disease, 12% vasculitis and 2% another I-RMD (table 2). The most common I-RMDs were rheumatoid arthritis (33%), axial spondyloarthritis (11%) and psoriatic arthritis (10%). Osteoarthritis (5%) and osteoporosis (2%) were the most frequent NI-RMDs.

The majority of the I-RMD group had minimal (41%) or low (28%) disease activity, although these data were missing in 17% of cases.

Fifty-four per cent of the I-RMD group received csDMARDs, 42% bDMARDs and 35% immunosuppressants. The most common individual medications were methotrexate (MTX; 34%), GCs (30%) and TNF-inhibitors (25%). Overall, there were few medication changes either before or after vaccination; however, changes were more prevalent in some drugs than others. Seven per cent of patients taking rituximab and IL-6 inhibitors held their medication before vaccination, 6% of TNF-inhibitor patients held the drug prior to vaccination and 6% and 4% of MTX cases held the medication before and after vaccination, respectively (table 2).

Vaccine information

Most patients received the Pfizer/BioNTech vaccine (70%), 17% had the AstraZeneca/Oxford and 8% the Moderna vaccine (table 3). One quarter of cases had one vaccine dose, whereas almost three quarters (74%) had two and 1% had three. Mean time between the first and second dose of the vaccine (if applicable) was 34 days (SD 62), 33 days (SD 18) in the I-RMD group and 43 days (SD 189) in the NI-RMD group. Mean time between the first and second vaccine doses in the Pfizer group was 28 days (SD 12), 30 days (SD 8) in the Moderna group and 78 days (SD 14) in the AstraZeneca/Oxford group.

The split of vaccine types, doses and postvaccination SARS-CoV-2 infection was similar between the I-RMD and NI-RMD groups (table 3), although 12 I-RMD cases received a combination of vaccines (Pfizer/BioNTech and either AstraZeneca/Oxford or CoronaVac/Sinovac).

SARS-CoV-2 infection after vaccination occurred in 46 cases (0.9%), with 42 cases occurring in the I-RMD (0.9%) and 4

Table 1 Patient demographics

		Inflammatory RMDs	Non-inflammatory RMDs	All patients
Total number		**4604**	**517**	**5121**
Gender	Female	3152 (68)	398 (77)	3550 (70)
	Male	1410 (31)	117 (23)	1527 (30)
	Other/unknown	42 (1)	2 (<1)	44 (1)
Age (years)	Mean (SD)	60.5 (15.1)	71.4 (12.5)	61.6 (15.2)
	Range (min to max)	15 to 96	22 to 98	15 to 98
Age categories (years)	<18	6 (<1)	–	6 (<1)
	18–40	526 (11)	11 (2)	537 (10)
	41–60	1640 (36)	94 (18)	1734 (34)
	61+	2432 (53)	412 (80)	2844 (56)
Country	Belgium	197 (4)	3 (1)	200 (4)
	France	1838 (40)	232 (45)	2070 (40)
	Italy	615 (13)	194 (38)	809 (16)
	Latvia	107 (2)	19 (4)	126 (2)
	Monaco	296 (6)	36 (7)	332 (6)
	Portugal	737 (16)	–	737 (14)
	Ireland	76 (2)	7 (1)	83 (2)
	Romania	61 (1)	4 (1)	65 (1)
	Slovak Republic	204 (4)	11 (2)	215 (4)
	Spain	164 (4)	5 (1)	169 (3)
	Turkey	78 (2)	1 (<1)	79 (2)
	UK	72 (2)	1 (<1)	73 (1)
	Other countries*	159 (3)	4 (1)	163 (3)

All values are n (%) unless stated otherwise.
*Other countries classified as those who submitted <50 cases: Albania, Australia, Austria, Croatia, Czechia, Estonia, Germany, Greece, Hungary, Lithuania, Luxembourg, Netherlands, Republic of Moldova, Russian Federation, Slovenia, Switzerland, Ukraine and USA.
RMDs, rheumatic and musculoskeletal diseases.

cases occurring in the NI-RMD group (0.8%); however, only 21 cases (0.7%) occurred in fully vaccinated patients (n=18, 0.7%; n=3, 1.1%; in the I-RMD and NI-RMD group, respectively).

When stratified by vaccine type, the percentage of cases with postvaccination SARS-CoV-2 infection was equal across vaccine types in the I-RMD group (online supplemental table 1) but only reported following the Pfizer/BioNTech vaccine or other vaccine types in the NI-RMD group (online supplemental table 2), though this is explained by the low number of cases vaccinated with Oxford/AstraZeneca and Moderna in the NI-RMD group.

Flares

Flare following vaccination was reported in 4.4% (n=204) of I-RMD cases, though these data were missing in 15% of cases. Mean time between the most recent vaccine dose (prior to flare) and the flare was 6 days (SD 8). The most common flares were arthritis flare, polyarthralgia and increase in fatigue (2.1%, 1.8%, and 0.7% of the I-RMD cohort, respectively). Most flares were mild (1.5%) or moderate (2.1%), with 29 cases (0.6%) being severe and 68 cases (1.5%) having started a new medication or increased existing medication dosage as a result of the flare (table 3).

The percentage of cases reporting a flare, flare severity and medication changes due to the flare were consistent among different vaccines (online supplemental table 1). The percentage of flares was slightly higher in patients with moderate/high disease activity (5.2%) compared with patients in remission/low disease disease activity (4.8%), with similar results observed for severe flares (1.0% vs 0.7%), though disease activity information was missing in 17% of cases. These findings raise the possibility of an association between higher disease activity and higher flare rate.

When stratified by I-RMD group (table 4), patients with inflammatory joint diseases experienced a slightly higher percentage of flares compared with the connective tissue disease and vasculitis groups (5.1% vs 3.1% vs 3.2%, respectively). Flare prevalence was similar across most medication groups in I-RMD cases (table 5), although patients on monotherapy or combination therapies of TNF-inhibitors (5.5%), other biologicals (5.3%), other csDMARDs (excluding methotrexate) (4.7%) and tsDMARDs (4.6%) reported a slightly higher percentage of flares than other medication groups (2.7%–3.6%). The lower flare rate was observed for rituximab and immunosuppressants (both 2.7%).

Adverse events

There were possible/probable vaccine-related AEs in 37% of all cases, 37% in the I-RMD group and 40% in the NI-RMD group. The majority were early AEs, mostly pain at injection site (19%), fatigue (12%), generalised muscle pain (7%) and fever (7%). Overall, the pattern and proportion of early AEs was similar between I-RMD and NI-RMD cases (table 3).

When I-RMD cases were stratified by vaccine type (online supplemental table 1), the percentage of AEs was similar across the group (32%–37%), except for Moderna, where a slightly higher percentage was observed (42%). The percentages of most individual types of early AEs were also similar across vaccines; however, a larger proportion of Moderna (26%) and a lower proportion of AstraZeneca/Oxford cases (12%) had pain at the injection site, and higher percentages of AstraZeneca/Oxford

Table 2 Rheumatic and musculoskeletal disease information

Primary RMD diagnosis	**Inflammatory RMDs**	**4604 (90)**
	Inflammatory joint diseases	**2979 (58)**
	Rheumatoid arthritis	1686 (33)
	Axial spondyloarthritis (including ankylosing spondylitis)	573 (11)
	Psoriatic arthritis	505 (10)
	Other peripheral spondyloarthritis (including reactive arthritis)	114 (2)
	Juvenile idiopathic arthritis, not systemic	23 (<1)
	Systemic juvenile idiopathic arthritis	7 (<1)
	Other inflammatory arthritis	70 (1)
	Connective tissue diseases	**928 (18)**
	Systemic lupus erythematosus	367 (7)
	Primary anti-phospholipid syndrome	26 (1)
	Sjogren's syndrome	223 (4)
	Systemic sclerosis	162 (3)
	Idiopathic inflammatory myopathy (myositis)	69 (1)
	Mixed connective tissue disease	37 (1)
	Undifferentiated connective tissue disease	43 (1)
	Ehlers-Danlos syndromes	1 (<1)
	Vasculitis	**593 (12)**
	Large vessel vasculitis – Takayasu arteritis	14 (<1)
	Large vessel vasculitis – giant cell arteritis	141 (3)
	Polymyalgia rheumatica	239 (5)
	Medium-vessel vasculitis (polyarteritis nodosa, Kawasaki disease)	11 (<1)
	ANCA-associated vasculitis (MP, GPA, EGPA)	127 (2)
	Immune complex small vessel vasculitis	7 (<1)
	Behcet's syndrome	33 (1)
	Other vasculitis	21 (<1)
	Other immune-mediated inflammatory diseases	**106 (2)**
	Monogenic autoinflammatory syndrome	13 (<1)
	Non-monogenic autoinflammatory syndrome	12 (<1)
	IgG4-related disease	16 (<1)
	Sarcoidosis	56 (1)
	Relapsing polychondritis	7 (<1)
	Chronic recurrent multifocal osteomyelitis	2 (<1)
	Non-inflammatory RMDs	**517 (10)**
	Gout or other crystal arthritis	62 (1)
	Osteoporosis	112 (2)
	Osteoarthritis	240 (5)
	Fibromyalgia	36 (1)
	Chronic mechanical back pain	16 (<1)
	Radiculopathy or regional pain	7 (<1)
	Other mechanical RMD (eg, tendinitis and bursitis)	44 (1)
Rheumatic disease activity (only applicable to patients with inflammatory RMD; n=4604)	Remission or inactive disease	1867 (41)
	Minimal or low disease activity	1276 (28)
	Moderate disease activity	610 (13)
	Severe or high disease activity	76 (2)
	Missing/unknown	775 (17)
Medication exposure at the time of vaccination (only applicable to patients with inflammatory RMD; n=4604)	**csDMARDS**	**2497 (54)**
	Antimalarials (including hydroxychloroquine and chloroquine)	568 (12)
	Held before vaccination	*2*
	Reduced before vaccination	*1*
	Held after vaccination	*3*
	Reduced after vaccination	*2*
	Leflunomide	211 (5)
	Held before vaccination	*7*
	Reduced before vaccination	*1*
	Held after vaccination	*2*
	Methotrexate	1557
	Held before vaccination	*58*
	Reduced before vaccination	*3*
	Held after vaccination	*90*
	Reduced after vaccination	*1*
	Sulfasalazine	161 (4)
	Held before vaccination	*1*
	Held after vaccination	*1*
	Reduced after vaccination	*1*
	bDMARDS	**1944 (42)**
	Abatacept	103 (2)
	Held before vaccination	*5*
	Held after vaccination	*3*
	Belimumab	32 (1)
	Held before vaccination	*2*
	Rituximab	260 (6)
	Held before vaccination	*18*
	Reduced before vaccination	*2*
	Held after vaccination	*1*
	Reduced after vaccination	*1*
	IL-1 inhibitors (including anakinra, canakinumab, rilonacept)	19 (<1)
	IL-6 inhibitors (including tocilizumab and sarilumab)	222 (5)
	Held before vaccination	*16*
	Held after vaccination	*4*
	Reduced after vaccination	*1*
	IL-12/23 inhibitors (including ustekinumab)	34 (1)
	Held before vaccination	*2*
	IL-23 inhibitors (guselkumab, risankizumab and tildrakizumab)	2 (<1)
	IL-17 inhibitors (including secukinumab, ixekizumab and brodalumab)	99 (2)
	Held before vaccination	*4*
	Held after vaccination	*4*
	Reduced after vaccination	*1*
	TNF-inhibitors (including adalimumab, certolizumab, etanercept, golimumab, infliximab and biosimilars)	1173 (25)
	Held before vaccination	*67*
	Reduced before vaccination	*5*
	Held after vaccination	*29*
	Reduced after vaccination	*2*
	tsDMARDS	**175 (4)**
	Apremilast	13 (<1)
	JAK inhibitors (including tofacitinib, baricitinib and upadacitinib)	162 (4)
	Held before vaccination	*5*
	Reduced before vaccination	*1*
	Held after vaccination	*10*
	Immunosuppressants	**1621 (35)**
	Glucocorticoids (systemic)	1385 (30)
	Held before vaccination	*6*
	Reduced before vaccination	*6*
	Held after vaccination	*6*
	Reduced after vaccination	*9*
	Azathioprine/6-mercaptopurine	88 (2)
	Held before vaccination	*2*
	Cyclosporine	15 (<1)
	Held before vaccination	*2*
	Reduced before vaccination	*1*
	Cyclophosphamide	8 (<1)
	Mycophenolate mofetil/mycophenolic acid	123 (3)
	Held before vaccination	*6*
	Held after vaccination	*2*
	Reduced after vaccination	*1*
	Tacrolimus	2 (<1)
	Other	**78 (2)**
	Intravenous immunoglobulin	15 (<1)
	Held after vaccination	*1*
	Antifibrotics (pirfenidone and nintedanib)	5 (<1)
	Thalidomide/lenalidomide	2 (<1)
	Colchicine	24 (<1)
	Denosumab	26 (1)
	Mepolizumab	4 (<1)
	Pembrolizumab	1 (<1)
	Vedolizumab	1 (<1)
	Unknown/missing	**43 (1)**
	None	**393 (9)**

All values are n (%) unless stated otherwise.
ANCA, anti-neutrophil cytoplasmic antibody; bDMARDs, biological disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; IL, interleukin; JAK, Janus kinase; MP, microscopic polyangiitis; TNF, tumour necrosis factor; tsDMARDs, targeted synthetic disease-modifying antirheumatic drug.

Table 3 COVID-19 vaccines, SARS-CoV-2 infections after vaccination, flares and adverse events in patients with inflammatory and non-inflammatory RMDs

		Inflammatory RMDs	Non-inflammatory RMDs	All patients
Vaccine	mRNA/nucleic acid (Pfizer/BioNTech)	3218 (70)	382 (74)	3600 (70)
	mRNA/nucleic acid (Moderna)	398 (7)	30 (6)	428 (8)
	Viral vector (AstraZeneca/Oxford)	759 (16)	96 (19)	855 (17)
	Viral vector (Janssen/Johnson & Johnson)	45 (1)	5 (1)	50 (1)
	Viral vector (Sputnik V)	5 (<1)	1 (<1)	6 (<1)
	Inactivated vaccine (CoronaVac/Sinovac)	53 (1)	1 (<1)	54 (1)
	Other	4 (<1)		4 (<1)
	Unknown/missing	110 (2)	2 (<1)	112 (2)
	Vaccine combination (Pfizer/BioNTech and AstraZeneca/Oxford)	11 (<1)		11 (<1)
	Vaccine combination (Pfizer/BioNTech and CoronaVac/Sinovac)	1 (<1)		1 (<1)
Vaccine doses	One	1149 (25)	132 (26)	1281 (25)
	Two	3406 (74)	384 (74)	3790 (74)
	Three	46 (1)	1 (<1)	47 (1)
	Unknown/missing	3 (<1)		3 (<1)
SARS-CoV-2 infection after vaccination	Yes	42 (1)	4 (1)	46 (1)
	No	4380 (95)	490 (95)	4870 (95)
	Unknown/missing	182 (4)	23 (4)	205 (4)
Vaccination status	Fully vaccinated cases	2622 (57)	270 (52)	2892 (56)
	Partially vaccinated cases	1982 (43)	247 (48)	2229 (44)
SARS-CoV-2 infection after vaccination, according to vaccination status (vaccination status is the denominator)	Fully vaccinated cases	18/2622 (1)	3/270 (1)	21/2892 (1)
	Partially vaccinated cases	24/1982 (1)	1/247 (<1)	25/2229 (1)
Flare following vaccination (only applicable to patients with inflammatory RMD; n=4604)	Yes	204 (4)	–	–
	No	3706 (81)	–	–
	Unknown/missing	694 (15)	–	–
Type of flare (data presented as percentage of total number of inflammatory RMD cases (n=4604))	Fever	18 (<1)	–	–
	Weight loss	1 (<1)	–	–
	Increase in fatigue	30 (1)	–	–
	Increase in dryness	4 (<1)	–	–
	Enlarged lymph nodes	4 (<1)	–	–
	Polyarthralgia	83 (2)	–	–
	Arthritis flare	95 (2)	–	–
	Cutaneous flare	16 (<1)	–	–
	Pulmonary flare	3 (<1)	–	–
	Renal flare	1 (<1)	–	–
	Neurological flare	2 (<1)	–	–
	Muscular flare	15 (<1)	–	–
	Cardiac flare	3 (<1)	–	–
	Gastro-intestinal flare	1 (<1)	–	–
	Haematological flare	3 (<1)	–	–
	Other	17 (<1)	–	–
	Unknown/missing	7 (<1)	–	–
Severity of flare (data presented as percentage of total number of inflammatory RMD cases (n=4604))	Mild/minor	69 (2)	–	–
	Moderate	98 (2)	–	–
	Severe/major without hospitalisation	20 (<1)	–	–
	Severe/major with hospitalisation	9 (<1)	–	–
	Unknown/missing	8 (<1)	–	–
	New medication or dosage increase due to flare	68 (1)	–	–
Vaccine-related AEs	Yes	1688 (37)	206 (40)	1894 (37)
	No	2916 (63)	311 (60)	3227 (63)

Continued

Table 3 Continued

		Inflammatory RMDs	Non-inflammatory RMDs	All patients
Early AEs	Pain at injection site	881 (19)	75 (15)	956 (19)
	Redness at injection site	70 (2)	4 (1)	74 (1)
	Swelling at injection site	75 (2)	1 (<1)	76 (1)
	Generalised muscle pain	302 (7)	41 (8)	343 (7)
	Generalised joint pain	163 (4)	26 (5)	189 (4)
	Headache	293 (6)	36 (7)	329 (6)
	Fever	331 (7)	44 (9)	375 (7)
	Chills	130 (3)	16 (3)	146 (3)
	Fatigue	531 (12)	65 (13)	596 (12)
	Vomiting	58 (1)	4 (1)	62 (1)
	Diarrhoea	38 (1)	4 (1)	42 (1)
	Unknown	5 (<1)		5 (<1)
AEs of special interest	Cardiovascular – arterial hypertension	4 (<1)	2 (<1)	6 (<1)
	Cardiovascular – arrhythmia	3 (<1)		3 (<1)
	Cardiovascular – coronary artery disease	2 (<1)		2 (<1)
	Cardiovascular – myocarditis and pericarditis	1 (<1)		1 (<1)
	Dermatologic – eczema, nodes and plaques	4 (<1)		4 (<1)
	Dermatologic – pruritus, injection site reaction, redness and burning	3 (<1)	2 (<1)	5 (<1)
	Gastrointestinal – liver injury	3(<1)	3 (1)	6 (<1)
	General conditions – hot flush, anxiety, lowered body temperature, loss and lack of appetite and night sweats	8 (<1)	1 (<1)	9 (<1)
	Haematological – peripheral deep vein thrombosis	2 (<1)		2 (<1)
	Haematological – haemorrhagic disease	1 (<1)		1 (<1)
	Haematological – thrombocytopenia	1 (<1)		1 (<1)
	Haematological – stroke	1 (<1)		1 (<1)
	Immunological – anaphylaxis	3 (<1)		3 (<1)
	Immunological – arthritis	4 (<1)	5 (1)	9 (<1)
	Immunological – skin and mucosal	8 (<1)	1 (<1)	9 (<1)
	Immunological – vasculitides	1 (<1)	2 (<1)	3 (<1)
	Lymphadenopathy	4 (<1)	2 (<1)	5 (<1)
	Malaise, fatigue and insomnia	5 (<1)	1 (<1)	6 (<1)
	Neurological – anosmia and ageusia	1 (<1)		1 (<1)
	Neurological – drowsiness, vertigo, dizziness, nausea, tinnitus, migraine and hallucination	21 (<1)	7 (1)	21 (<1)
	Other possible cardiac symptoms – ankle oedema, dyspnoea and dry cough	7 (<1)	2 (<1)	9 (<1)
	Pain/pain syndromes	2 (<1)	2 (<1)	4 (<1)
	Tendons and joints – tendinopathy, frozen shoulder and carpal tunnel syndrome	4 (<1)	2 (<1)	6 (<1)
	Viral infection – herpes, herpes zoster and shingles	9 (<1)	1 (<1)	10 (<1)
	Viral infection – influenza, flu-like episodes, rhinitis, cough and cold	7 (<1)	1 (<1)	8 (<1)
	Other	3 (<1)	3 (1)	6 (<1)
	Total of adverse events of special interest	112 (2)	37 (7)	149 (3)
AE seriousness	Non-serious	90 (2)	25 (5)	115 (2)
	Serious – important medical event	8 (<1)	8 (2)	16 (<1)
	Serious - hospitalisation (or prolongation of existing hospitalisation)	6 (<1)	2 (<1)	8 (<1)
	Serious – life threatening	3 (<1)		3 (<1)
	Unknown/missing	4 (<1)		4 (<1)
AE outcome	Ongoing/continuing	21 (<1)	6 (1)	27 (1)
	Recovered/resolved without sequelae	75 (1)	25 (5)	100 (2)
	Recovered/resolved with sequelae	6 (<1)	2 (<1)	8 (<1)
	Unknown/missing	9 (<1)	1 (<1)	10 (<1)

All values are n (%) unless stated otherwise.
AEs, adverse events; RMDs, rheumatic and musculoskeletal diseases.

Table 4 Flares and AEs stratified by inflammatory RMD disease group

		Inflammatory joint diseases (n=2977)	Connective tissue diseases (n=928)	Vasculitis (n=593)
Flare following vaccination	Yes	151 (5)	29 (3)	19 (3)
	No	2260 (76)	784 (85)	561 (95)
	Unknown/missing	566 (19)	115 (12)	13 (2)
Severity of flare	Mild/minor	51 (2)	13 (1)	5 (1)
	Moderate	77 (3)	12 (1)	8 (1)
	Severe/major without hospitalisation	15 (1)	1 (<1)	3 (1)
	Severe/major with hospitalisation	1 (<1)	2 (<1)	3 (1)
	Unknown/missing	7 (<1)	1 (<1)	
	New medication or dosage increase due to flare	44 (1)	10 (1)	11 (2)
Vaccine-related AEs	Yes	1092 (37)	382 (41)	175 (30)
	No	1885 (63)	546 (59)	418 (70)
AE severity (only collected for AEs of special interest)	Non-serious	55 (2)	21 (2)	13 (2)
	Severe – important medical event	4 (1)	4 (1)	
	Severe – hospitalisation (or prolongation of existing hospitalisation)	4 (1)		2 (<1)
	Severe – life threatening	2 (<1)	1 (<1)	
	Unknown/missing	2 (<1)		

All values are n (%) unless stated otherwise.
AEs, adverse events; RMD, rheumatic and musculoskeletal disease.

(12%) and Moderna (11%) cases had fever following vaccination (in comparison with 6% with other vaccines).

Forty-one per cent of connective tissue disease cases reported AEs, compared with 37% of inflammatory joint disease and 30% of vasculitis cases (table 4). When I-RMD cases were stratified by medication group (table 5), all groups reported similar AE percentages, expect for patients on other csDMARDs (42% vs 33%–35%).

In the NI-RMD group (online supplemental table 2), the prevalence of AEs was more variable across vaccine types, with

Table 5 Flares and adverse events in patients with inflammatory RMDs, stratified by medication

		MTX mono/ combi (no biologicals or tsDMARDs) (n=895)	Other csDMARD mono/ combi (no biologicals or tsDMARDs) (n=657)	TNF mono/ combi (n=1173)	RTX mono/ combi (n=260)	Other biologics mono/ combi (n=511)	tsDMARD mono/ combi (n=175)	Immunosuppressants mono/combi (no biologics or tsDMARDs) (n=995)
Flare following vaccination	Yes	32 (4)	31 (5)	65 (6)	7 (3)	27 (5)	8 (5)	27 (3)
	No	765 (85)	520 (79)	799 (68)	204 (78)	415 (81)	150 (86)	870 (87)
	Unknown/missing	98 (11)	106 (16)	309 (26)	49 (19)	69 (14)	17 (10)	98 (10)
Severity of flare	Mild/minor	13 (1)	14 (2)	19 (2)	3 (1)	6 (1)	4 (2)	11 (1)
	Moderate	14 (2)	11 (2)	39 (3)	1 (<1)	17 (3)	3 (2)	8 (1)
	Severe/major without hospitalisation	1 (<1)	3 (<1)	4 (<1)	1 (<1)	1 (<1)		2 (<1)
	Severe/major with hospitalisation	2 (<1)	2 (<1)		1 (<1)			6 (<1)
	Unknown/missing	2 (<1)	1 (<1)	3 (<1)	1 (<1)	3 (1)	1 (1)	
	New medication or dosage increase due to flare	12 (1)	11 (2)	16 (1)	1 (<1)	8 (2)		15 (2)
Vaccine-related AEs	Yes	314 (35)	276 (42)	412 (35)	87 (33)	172 (34)	61 (35)	352 (35)
	No	581 (65)	381 (58)	761 (65)	173 (67)	339 (66)	114 (65)	643 (65)
AE severity (only collected for AEs of special interest)	Non-serious	12 (1)	16 (2)	13 (1)	2 (1)	17 (3)	3 (2)	19 (2)
	Severe – Important medical event	1 (<1)	3 (<1)	1 (<1)		1 (<1)	3 (2)	4 (<1)
	Severe - Hospitalisation (or prolongation of existing hospitalisation)	1 (<1)	1 (<1)			1 (<1)	1 (1)	2 (<1)
	Severe - Life-threatening		1 (<1)		1 (<1)	1 (<1)		1 (<1)
	Missing	1 (<1)		2 (<1)				

All values are N (%) unless stated otherwise.

AEs, adverse events; combi, combination therapy; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; mono, monotherapy; MTX, methotrexate; RMD, rheumatic and musculoskeletal disease; RTX, rituximab; TNF, tumour necrosis factor; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

the most salient difference between vaccines being the lower percentages of Pfizer/BioNTech (13%) and AstraZeneca/Oxford (10%) cases that experienced pain at injection site compared with 50% of Moderna vaccinated cases.

There were 149 AEs of special interest (2.9% of all patients), 112 (2.4%) in the I-RMD group and 37 (7.2%) in the NI-RMD group, and most of the AEs resolved/recovered without sequelae (100 cases, 2.0% of all patients; n=75, 1.6% in the I-RMD group; n=25, 4.8% in the NI-RMD group). Both in the I-RMD and NI-RMD group, a larger diversity of AEs of special interest were seen following vaccination with Pfizer/BioNTech, reflecting the higher number of cases receiving this vaccine. However, there were no salient differences between vaccines or between patients with I-RMD and NI-RMD (table 6). Mean time between the most recent vaccine dose (prior to AE of special interest) and the AE of special interest was 7 days (SD 17), 7 days (SD 15) in the I-RMD group and 8 days (SD 21) in the NI-RMD group.

SAEs were rare (n=27, 0.5% of all patients) and more prevalent in the NI-RMD group (n=10, 1.9%) than in the I-RMD group (n=17, 0.4%). Among these 27 SAEs, three were life threatening, all occurring in Pfizer/BioNTech vaccine recipients in the I-RMD group. These were two cases of 'cardiac – coronary artery disease' events and one 'gastrointestinal – liver injury' event; all three events recovered/resolved, though one cardiac event and the 'gastrointestinal – liver injury' event recovered/resolved with sequelae (table 6).

There were six instances of SAEs resulting in hospitalisation in the I-RMD group, all in Pfizer/BioNTech vaccine recipients. One of these was a 'haematologic – peripheral deep vein thrombosis' event, one was a 'haematologic – stroke' event, one was an 'immunological - skin or mucosal' event (erythema nodosum), two were 'viral infection – herpes zoster/shingles' events and finally one 'other - neck swelling event' (table 6).

Eight SAEs classified as serious important medical events were seen in the I-RMD group, occurring in Pfizer/BioNTech (n=7) and AstraZeneca/Oxford (n=1) vaccine recipients. There were three 'immunological - skin or mucosal' events (gingivitis, pharyngitis and bullous leg rash), one 'cardiac - arterial hypertension', one 'malaise', one 'neurological – hemiparesis', one 'other – possible cardiac' event (dyspnoea) and one 'viral infection – herpes zoster/shingles' event (table 7).

There were two SAEs resulting in hospitalisation in the NI-RMD group: one an 'immunological – vasculitides' event (giant cell arteritis), in a Moderna vaccine recipient, and one other possible cardiac event (dyspnoea), in a Pfizer/BioNTech vaccine recipient. Eight events were classified as important medical events: one 'arterial hypertension' event, two 'immunological – arthritis' events, a 'gastrointestinal – liver injury' event, one 'immunological – vasculitides' event (polymyalgia rheumatica-like syndrome), one 'neurological – syncope', one 'neurological – vertigo' and one 'tendons and joints' event (frozen shoulder) (table 7).

SAEs resulting in death, persistent or significant disability/incapacity or congenital anomaly/birth defect were neither reported in the I-RMD group nor in the NI-RMD group.

Of note, we are not aware of any cases of vaccine-induced immune thrombotic thrombocytopenia in this cohort, an exceedingly rare complication described in the general population with the AstraZeneca and Janssen vaccines. One case of isolated thrombocytopenia after the first dose of the AstraZeneca vaccine was reported in a young (<30 years old) female patient with mixed connective tissue disease; however, this was a transient laboratory change without clinical repercussion. Regarding myocarditis and pericarditis, a rare complication associated with mRNA vaccines, this was reported after the second dose of the Pfizer vaccine in a young (<30 years old) female patient with systemic lupus erythematosus, and she recovered without sequelae from this event.

DISCUSSION

We created the largest international case series of people with I-RMDs vaccinated against SARS-CoV-2 and report that the safety profile of vaccines against SARS-CoV-2 in this population was reassuring. The overwhelming majority of patients tolerated their vaccination well with rare reports of I-RMD flare (4.4%, 0.6% severe) and very rare reports of SAEs (0.4%). Changes in medication due to flare were also rare (1.5% of I-RMD patients). Most AEs were the same and in similar proportion as observed in patients with NI-RMDs (and the general population); they were non-serious and involved transient local and systemic symptoms.

Regarding flares, the data suggest that the risk of I-RMD flare following vaccination is low and not more strongly associated with any particular type of vaccine, with observed percentages being compatible with the natural history of the disease rather than necessarily caused by vaccines against SARS-CoV-2.[17]

Regarding early AEs (reactogenicity), both the profile and frequency of AEs were similar between I-RMD and NI-RMD cases. The frequency and type of early AEs was also similar between vaccines, both for the I-RMD and NI-RMD groups, with the possible exception of a slightly higher proportion of pain at the injection site with the Moderna vaccine (both in the I-RMD and NI-RMD group). Both the flare and AE data are in line with previous smaller studies in patients with I-RMDs (13 to 2860 patients, with the largest cohort being patient reported rather than physician reported).[18–40]

Regarding AEs of special interest, they were infrequent and their proportion tended to be smaller in the I-RMD group compared with the NI-RMD group and in line with rates reported in trials in the general population. There was significant diversity in terms of AEs of special interest observed both in I-RMD and NI-RMD cases, particularly in I-RMD cases, reflecting the higher number of cases in this subgroup of patients; however, no salient differences between the I-RMD and NI-RMD groups were found, and no clustering of AEs of special interest was observed.

While the primary aim of our study was to collect safety data among I-RMD patients receiving vaccines against SARS-CoV-2, we also collected data regarding breakthrough infections and found that these occurred very infrequently, particularly in fully vaccinated patients (0.7% and 1.1% of cases in the I-RMD and NI-RMD group, respectively). A more detailed report describing cases of breakthrough infections in patients with I-RMDs from the EULAR COVAX and COVID-19 registries, including details about vaccines administered, exposure to anti-rheumatic medications and outcome of breakthrough infections, has previously been published.[40]

We found that temporary discontinuation of antirheumatic medications was infrequent. This attitude towards antirheumatic medications might reflect the fact that this is largely a European registry. Contrary to the American College of Rheumatology, who recommended holding methotrexate, JAK inhibitors, abatacept, mycophenolate mofetil and rituximab in certain patients with controlled disease,[12] EULAR did not advise temporarily stopping or adjusting the timing of any of these medications (with the exception of rituximab) relative to when the vaccine against SARS-CoV-2 is administered.[11] Future studies are needed to determine if changes in certain antirheumatic medication

Table 6 Adverse events of special interest possibly/probably related to COVID-19 vaccination among patient with inflammatory RMDs

AE type	Seriousness of AE	Outcome of AE	COVID-19 vaccine	RMD	RMD medication*	Medication held or reduced
Cardiovascular – arterial hypertension	Non-serious	Recovered/resolved without sequelae	Moderna	axSpA	TNFi	No
	Non-serious	Recovered/resolved without sequelae	AZ	RA	HCQ+GC	No
	Non-serious	Recovered/resolved without sequelae	Pfizer	RA	MTX+GC	No
	Serious (important medical event)	Recovered/resolved without sequelae	Pfizer	pSpA	GC	No
Cardiac – arrhythmia	Non-serious	Recovered/resolved without sequelae	Pfizer	SLE	HCQ+AZA+GC	No
	Non-serious	UNK	Pfizer	RA	GC	Yes
	Non-serious	Ongoing/continuing	Pfizer	EDS	None	NA
Cardiac – coronary artery disease	Serious (life threatening)	Recovered/resolved without sequelae	Pfizer	RA	ABA+MTX+GC	No
	Serious (life threatening)	Recovered/resolved with sequelae	Pfizer	RA	RTX+LEF+GC	No
Cardiac – myocarditis and pericarditis	Non-serious	Recovered/resolved without sequelae	Pfizer	SLE	None	NA
Dermatological – eczema, nodes and plaques	Non-serious	Recovered/resolved without sequelae	Pfizer	RA	ABA	No
	Non-serious	Recovered/resolved without sequelae	Moderna	SjS	HCQ+GC	Yes
	Non-serious	Ongoing/continuing	AZ	PsA	Apremilast	No
	Non-serious	Recovered/resolved without sequelae	Pfizer	pSpA	TNFi	No
Dermatological – pruritus, injection site reaction, redness and burning	Non-serious	Recovered/resolved without sequelae	Pfizer	pSpA	LEF+GC	No
	Non-serious	Ongoing/continuing	Pfizer	RA	MTX+GC	No
	Non-serious	Recovered/resolved without sequelae	Pfizer	PMR	HCQ+GC	No
Gastrointestinal – liver injury	Non-serious	Recovered/resolved without sequelae	Pfizer	GCA	MTX	Yes
	Non-serious	Ongoing/continuing	Pfizer	RP	AZA+GC	No
	Serious (life threatening)	Recovered/resolved with sequelae	Pfizer	SLE	HCQ+GC	No
General conditions – hot flush, anxiety, lowered body temperature, loss and lack of appetite and night sweats	Non-serious	Recovered/resolved without sequelae	Pfizer	SSc	MMF+GC	No
	Non-serious	Recovered/resolved without sequelae	AZ	axSpA	TNFi	No
	Non-serious	Recovered/resolved without sequelae	Pfizer	RA	IL-6	UNK
	Non-serious	Recovered/resolved without sequelae	Pfizer	PsA	IL-17	Yes
	Non-serious	Recovered/resolved without sequelae	Pfizer	GCA	None	NA
	Non-serious	Recovered/resolved without sequelae	AZ	RA	ABA+MTX	No
	Non-serious	Recovered/resolved without sequelae	Moderna	RA	None	NA
	Non-serious	Ongoing/continuing	AZ	axSpA	TNFi	No
Haematological – peripheral deep vein thrombosis	Non-serious	Ongoing/continuing	Pfizer	axSpA	IL-17	No
	Serious (hospitalisation)	Ongoing/continuing	Pfizer	AAV	AZA+GC	No
Haematological – haemorrhagic disease	Non-serious	Recovered/resolved without sequelae	AZ	RA	HCQ+GC	No
Haematological – stroke	Serious (Hospitalisation)	Recovered/resolved with sequelae	Pfizer	PMR	IL-6+GC	No
Haematological – thrombocytopenia	Non-serious	Recovered/resolved without sequelae	AZ	mCTD	None	NA
Immunological – anaphylaxis	Non-serious	Recovered/resolved without sequelae	Pfizer	RA	MTX	No
	Non-serious	Recovered/resolved without sequelae	Pfizer	SSc	Sildenafil	No
	Non-serious	Recovered/resolved without sequelae	AZ	Other vasculitis	GC	Yes
Immunological – arthritis	Non-serious	Recovered/resolved without sequelae	AZ	SjS	HCQ	No
	Non-serious	Recovered/resolved without sequelae	Pfizer	PMR	HCQ+GC	No
	Non-serious	UNK	AZ	GCA	IL-6+GC	No
	Non-serious	Recovered/resolved without sequelae	Pfizer	SLE	HCQ+Belimumab	No
Immunological – skin or mucosal	Non-serious	Recovered/resolved without sequelae	Pfizer	SLE	AZA+GC	No
	Non-serious	Recovered/resolved without sequelae	Pfizer	axSpA	SSZ+GC+NSAIDs	No
	Non-serious	Recovered/resolved without sequelae	Pfizer	Myositis	HCQ+MTX+GC	No
	Non-serious	Ongoing/continuing	Moderna	SjS	None	NA
	Serious (hospitalisation)	Recovered/resolved without sequelae	Pfizer	PsA	None	NA
	Serious (important medical event)	Recovered/resolved without sequelae	Pfizer	RA	ABA+HCQ	No
	Serious (important medical event)	Recovered/resolved without sequelae	AZ	u-CTD	HCQ	No
	Serious (important medical event)	Ongoing/continuing	Pfizer	PsA	TNFi	No
Immunological – vasculitides	Non-serious	Recovered/resolved without sequelae	Pfizer	PsA	IL-17	Yes

Continued

Table 6 Continued

AE type	Seriousness of AE	Outcome of AE	COVID-19 vaccine	RMD	RMD medication*	Medication held or reduced
Lymphadenopathy	Non-serious	Recovered/resolved without sequelae	Pfizer	PsA	IL-17+MTX	No
	Non-serious	Recovered/resolved without sequelae	Moderna	mCTD	None	NA
	Non-serious	Recovered/resolved without sequelae	Pfizer	Other vasculitis	None	NA
	Non-serious	Ongoing/continuing	Pfizer	RA	MTX	No
Malaise, fatigue and insomnia	Non-serious	Recovered/resolved without sequelae	AZ	PMR	MTX+GC	No
	Non-serious	Recovered/resolved with sequelae	AZ	Monogenic AIS	Colchicine	No
	Serious (important medical event)	Ongoing/continuing	Pfizer	SSc	MMF	Yes
	UNK	UNK	Pfizer	PsA	None	NA
	UNK	UNK	Pfizer	PsA	TNFi+NSAIDs	No
Neurological – anosmia and ageusia	Non-serious	Recovered/resolved without sequelae	Pfizer	SjS	MTX	No
Neurological – drowsiness, vertigo, dizziness, nausea, tinnitus, migraine, hallucination and hemiparesis	Non-serious	Ongoing/continuing	Pfizer	Sarcoidosis	HCQ	No
	Non-serious	Recovered/resolved without sequelae	Unknown	Other IA	HCQ+GC	No
	Non-serious	Recovered/resolved without sequelae	Pfizer	pSpA	Apremilast	No
	Non-serious	Recovered/resolved without sequelae	AZ	pSpA	IL-17	No
	Non-serious	Recovered/resolved without sequelae	Pfizer	PsA	IL-17	No
	Non-serious	Recovered/resolved without sequelae	Pfizer	axSpA	IL-17	No
	Non-serious	Recovered/resolved without sequelae	Pfizer	SjS	MTX	No
	Non-serious	Recovered/resolved without sequelae	Pfizer	PsA	MTX	No
	Non-serious	Recovered/resolved without sequelae	Moderna	RA	SSZ	No
	Non-serious	Recovered/resolved without sequelae	Pfizer	axSpA	TNFi	No
	Non-serious	Recovered/resolved without sequelae	Pfizer	Non-systemic JIA	TNFi	No
	Non-serious	Recovered/resolved without sequelae	Pfizer	axSpA	TNFi	No
	Non-serious	Recovered/resolved without sequelae	Pfizer	PsA	TNFi	No
	Non-serious	Recovered/resolved without sequelae	Pfizer	axSpA	TNFi	Yes
	Non-serious	Recovered/resolved without sequelae	Moderna	pSpA	None	NA
	Non-serious	Recovered/resolved without sequelae	Pfizer	PsA	IL-12/23	No
	Non-serious	Ongoing/continuing	AZ	PsA	None	NA
	Non-serious	Recovered/resolved without sequelae	AZ	RA	SSZ	No
	Non-serious	Recovered/resolved without sequelae	Pfizer	RA	MTX	Yes
	Non-serious	Recovered/resolved without sequelae	Pfizer	SSc	Unknown	NA
	Serious (important medical event)	Ongoing/continuing	Pfizer	SSc	HCQ+MMF	No (HCQ), UNK (MMF)
Other possible cardiac symptoms – ankle oedema, dyspnoea and dry cough	Non-serious	Recovered/resolved without sequelae	Pfizer	PsA	IL-17	No
	Non-serious	Recovered/resolved without sequelae	Moderna	RA	IL-6	No
	Non-serious	Recovered/resolved with sequelae	Pfizer	AAV	Benralizumab	No
	Non-serious	Ongoing/continuing	Moderna	RA	RTX+GC	No
	Non-serious	Recovered/resolved without sequelae	Pfizer	RA	JAKi +GC	Yes (GC), No (JAKi)
	Serious (important medical event)	Recovered/resolved without sequelae	Pfizer	SjS	HCQ	No
	UNK	UNK	Pfizer	RA	TNFi	No
Pain/pain syndromes	Non-serious	UNK	Pfizer	SjS	None	NA
	Non-serious	Recovered/resolved without sequelae	Pfizer	PMR	GC	UNK
Tendons and joints – tendinopathy, frozen shoulder and carpal tunnel syndrome	Non-serious	UNK	Pfizer	RA	ABA+MTX	No
	Non-serious	Ongoing/continuing	Moderna	uCTD	None	NA
	Non-serious	Ongoing/continuing	Pfizer	PMR	GC	No
	UNK	UNK	AZ	RA	MTX	No

Continued

Table 6 Continued

AE type	Seriousness of AE	Outcome of AE	COVID-19 vaccine	RMD	RMD medication*	Medication held or reduced
Viral infections – herpes, herpes zoster and shingles	Non-serious	Ongoing/continuing	Pfizer	SjS	HCQ	No
	Non-serious	Ongoing/continuing	Moderna	RA	JAKi	No
	Non-serious	Ongoing/continuing	Pfizer	RA	JAKi	No
	Non-serious	Recovered/resolved without sequelae	Pfizer	axSpA	TNFi	No
	Non-serious	Ongoing/continuing	Pfizer	PMR	GC	No
	Non-serious	Recovered/resolved with sequelae	AZ	RA	TNFi	No
	Serious (hospitalisation)	Recovered/resolved without sequelae	Pfizer	RA	JAKi	Yes
	Serious (hospitalisation)	UNK	Pfizer	RA	MTX+GC	Yes (MTX), No (GC)
	Serious (important medical event)	Recovered/resolved without sequelae	Pfizer	RA	MTX+GC	No
Viral infections – influenza, flu-like episodes, rhinitis, cough and cold	Non-serious	Recovered/resolved without sequelae	Pfizer+AZ	GCA	IL-6	No
	Non-serious	Recovered/resolved without sequelae	Pfizer	Myositis	MTX	No
	Non-serious	Recovered/resolved without sequelae	Pfizer	RA	MTX	No
	Non-serious	Recovered/resolved without sequelae	Pfizer	RA	RTX+MTX	No
	Non-serious	Recovered/resolved without sequelae	Pfizer	axSpA	TNFi	No
	Non-serious	Recovered/resolved without sequelae	Pfizer	CRMO	TNFi+MTX	No
	Non-serious	Recovered/resolved without sequelae	Pfizer	SjS	None	NA
Other – GORD	Non-serious	Recovered/resolved without sequelae	Pfizer	RA	LEF	No
Other – neck swelling	Serious (hospitalisation)	Recovered/resolved without sequelae	Pfizer	RA	LEF	No
Other (UNK)	Non-serious	UNK	Pfizer	RA	JAKi+LEF+GC	No

*Immunosuppressive or immunomodulatory medication.
AAV, ANCA-associated vasculitis; ABA, abatacept; AE, adverse event; AIS, autoinflammatory syndrome; axSpA, axial spondyloarthritis; AZ, Oxford/AstraZeneca; AZA, azathioprine; CRMO, chronic recurrent multifocal osteomyelitis; EDS, Ehlers-Danlos syndrome; GC, glucocorticoids; GCA, giant cell arteritis; GORD, gastro-oesophageal reflux disease; HCQ, hydroxychloroquine; IA, inflammatory arthritis; IL-6, interleukin-6; IL-17, interleukin-17; IL-12/23, interleukin-12/23; JAKi, Janus kinase inhibitors; JIA, juvenile idiopathic arthritis; LEF, leflunomide; mCTD, mixed connective tissue disease; MMF, mycophenolate mofetil/mycophenolic acid; MTX, methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs; PMR, polymyalgia rheumatica; PsA, psoriatic arthritis; pSpA, peripheral spondyloarthritis; RA, rheumatoid arthritis; RMD, rheumatic and musculoskeletal disease; RP, relapsing polychondritis; RTX, rituximab; SjS, Sjogren's syndrome; SLE, systemic lupus erythematosus; SpA, spondyloarthritis; SSc, systemic sclerosis; SSZ, sulfasalazine; TNFi, tumour necrosis factor; uCTD, undifferentiated connective tissue disease; UNK, unknown/missing.

regimens might increase the effectiveness of vaccines against SARS-CoV-2 while balancing the risk of disease flare (and the need for additional treatment of the flare, such as GCs).

Strengths of this study include the rapid dissemination via European networks (EULAR, ERN ReCONNET and ERN RITA) that resulted in a large number of cases reported by rheumatologists, internists or associated healthcare professionals over a short period of time. However, our study has important limitations. The COVAX registry relies on voluntary case submission, leading to possible selection bias in the data, and concerns regarding the generalisability of the results. However, this could in principle have led to over-reporting of flares and AEs; therefore the low rate of flares/AEs consistent with other publications is reassuring. Moreover, the underlying risk of flare also differs among RMDs, which may influence the overall flare rate and differences between conditions. Furthermore, dissemination was more effectively achieved in certain European countries (eg, France, Italy and Portugal), and reporting was also influenced by differences in vaccine availability and access across European countries, which has resulted in a significantly higher proportion of cases vaccinated with the Pfizer vaccine, limiting comparisons between vaccines. Time between vaccination and case reporting is also variable and sometimes relatively short, limiting data interpretation and not allowing us to draw any conclusions regarding the long-term safety profile of vaccines against SARS-CoV-2. Moreover, a control group of patients with I-RMDs is not available, and the sample size of patients with NI-RMDs is substantially smaller. For some signs/symptoms, it can be difficult to determine if the event should be considered an I-RMD flare or simply a transient side effect of the vaccine (eg, polyarthralgia); in our study, this decision was left to the reporting physician, which can be considered a study limitation. Similarly, systemic flares were also based on the report of the physician without collection of more detailed evidence of the flare (eg, results of investigations). Finally, the information regarding SARS-CoV-2 infection after vaccination is based on the report of physicians/healthcare providers, and no information is provided concerning the presence or the titre of postvaccine antibodies. Importantly, no causal conclusions regarding vaccination and the development of flares/AEs can firmly be drawn from this dataset.

In conclusion, our findings should provide reassurance to rheumatologists, other health professionals and vaccine recipients and and promote confidence in SARS-CoV-2 vaccine safety in people with I-RMDs. The rate of severe flares was very low (0.6%). Likewise, the rate of SAEs in I-RMDs was 0.4%, comparable and even lower than in patients with NI-RMDs (1.1%), suggesting that the tolerance to the vaccine was not different between the groups. Interestingly, in clinical trials of mRNA, inactivated and non-replicating vector vaccines against SARS-CoV-2 in the general population, the pooled rates of SAEs were very similar to our study, ranging from 0.4% to 0.6% in the vaccine group, and from 0.5% to 0.6% in the control group,[41] suggesting that these SAEs are not necessarily causally related to the vaccine and might be coincidental observations. However, although the mean time between first vaccine dose and case reporting of 66 days in our report is not very different from the follow-up period in some of the vaccination trials, this is an indirect comparison that should be interpreted with caution, because

Table 7 Adverse events of special interest possibly/probably related to COVID-19 vaccination among patient with non-inflammatory RMDs

AE type	Severity of AE	Outcome of AE	COVID-19 vaccine	RMD	RMD medication	Medication held or reduced
Cardiovascular –arterial hypertension	Serious (important medical event)	Recovered/resolved with sequelae	Pfizer	OA	None	NA
	Non-serious	Recovered/resolved without sequelae	Pfizer	Other mechanical RMD	None	NA
Dermatological – pruritus, injection site reaction, redness and burning	Non-serious	Recovered/resolved without sequelae	Moderna	OA	None	NA
	Non-serious	Recovered/resolved without sequelae	Pfizer	OA	None	NA
Gastrointestinal – liver injury	Non-serious	Ongoing/continuing	Pfizer	OA	None	NA
	Non-serious	UNK	Moderna	Osteoporosis	None	No
	Serious (important medical event)	Ongoing/continuing	AZ	Fibromyalgia	None	
General conditions – hot flush, anxiety, lowered body temperature, loss and lack of appetite and night sweats	Non-serious	Recovered/resolved without sequelae	AZ	OA	None	NA
Immunological – arthritis	Non-serious	Recovered/resolved without sequelae	Pfizer	Other mechanical RMD	None	NA
	Non-serious	Recovered/resolved without sequelae	Pfizer	Osteoporosis	None	NA
	Serious (important medical event)	Ongoing/continuing	AZ	OA	None	NA
	Serious (important medical event)	Recovered/resolved with sequelae	Pfizer	OA	None	NA
	Non-serious	Ongoing/continuing	Moderna	Other mechanical RMD	None	NA
Immunological – skin and mucosal	Non-serious	Recovered/resolved without sequelae	AZ	OA	None	NA
Immunological – vasculitides	Serious (hospitalisation)	Recovered/resolved without sequelae	Moderna	OA	None	NA
	Serious (important medical event)	Ongoing/continuing	Pfizer	OA	None	NA
Malaise, fatigue and insomnia	Non-serious	Recovered/resolved without sequelae	Pfizer	OA	Colchicine	No
Lymphadenopathy	Non-serious	Recovered/resolved without sequelae	Pfizer	OA	None	NA
	Non-serious	Recovered/resolved without sequelae	Pfizer	Osteoporosis	None	NA
Neurological – drowsiness, vertigo, dizziness, nausea, tinnitus, migraine, hallucination and hemiparesis	Non-serious	Recovered/resolved without sequelae	Moderna	Osteoporosis	None	NA
	Non-serious	Recovered/resolved without sequelae	Moderna	OA	None	NA
	Non-serious	Recovered/resolved without sequelae	Pfizer	Other mechanical RMD	None	NA
	Non-serious	Recovered/resolved without sequelae	Pfizer	Gout	None	NA
	Non-serious	Recovered/resolved without sequelae	AZ	Other mechanical RMD	None	NA
	Serious (important medical event)	Recovered/resolved without sequelae	Pfizer	Fibromyalgia	None	NA
	Serious (important medical event)	Recovered/resolved without sequelae	Pfizer	Fibromyalgia	None	NA
Other possible cardiac symptoms – ankle oedema, dyspnoea and dry cough	Non-serious	Recovered/resolved without sequelae	Pfizer	OA	HCQ	No
	Serious (hospitalisation)	Recovered/resolved without sequelae	Pfizer	Osteoporosis	None	NA
Pain/pain syndromes	Non-serious	Recovered/resolved without sequelae	AZ	OA	None	NA
	Non-serious	Recovered/resolved without sequelae	Pfizer	OA	None	NA
Tendons and joints – tendinopathy, frozen shoulder and carpal tunnel syndrome	Non-serious	Recovered/resolved without sequelae	AZ	Osteoporosis	None	NA
	Serious (Important medical event)	Ongoing/continuing	AZ	Chronic mechanical back pain	None	NA
Viral infections – herpes, herpes zoster and shingles	Non-serious	Recovered/resolved without sequelae	Pfizer	OA	None	NA
Viral infections – influenza, flu-like episodes, rhinitis, cough and cold	Non-serious	Recovered/resolved without sequelae	AZ	Osteoporosis	None	NA
Other – epistaxis	Non-serious	Recovered/resolved without sequelae	AZ	OA	None	NA
Other (UNK)	Non-serious	Recovered/resolved without sequelae	Moderna	Fibromyalgia	None	NA
Other (UNK)	Non-serious	Recovered/resolved without sequelae	Pfizer	Fibromyalgia	None	NA

*Immunosuppressive or immunomodulatory medication.

AZ, Oxford/AstraZeneca; HCQ, hydroxychloroquine; OA, osteoarthritis; RMD, rheumatic and musculoskeletal disease; UNK, unknown/missing.

the follow-up period in our study was allowed to vary, and there are also important differences between follow-up periods among vaccination trials (that typically do not go beyond 6 months). Future studies should address the effectiveness and safety of vaccines against SARS-CoV-2 in patients with I-RMDs and/or patients taking immunosuppressive/immunomodulatory drugs, both in controlled and general surveillance settings.

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