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Factors associated with disease flare following SARS-CoV-2 vaccination in people with inflammatory rheumatic and musculoskeletal diseases: results from the physician-reported EULAR Coronavirus Vaccine (COVAX) Registry

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ABSTRACT

Objectives To investigate the frequency and factors associated with disease flare following vaccination against SARS-CoV-2 in people with inflammatory/autoimmune rheumatic and musculoskeletal diseases (I-RMDs).

Methods Data from the European Alliance of Associations for Rheumatology Coronavirus Vaccine physician-reported registry were used. Factors associated with flare in patients with I-RMDs were investigated using multivariable logistic regression adjusted for demographic and clinical factors.

Results The study included 7336 patients with I-RMD, with 272 of 7336 (3.7%) experiencing flares and 121 of 7336 (1.6%) experiencing flares requiring starting a new medication or increasing the dosage of an existing medication. Factors independently associated with increased odds of flare were: female sex (OR=1.40, 95% CI=1.05 to 1.87), active disease at the time of vaccination (low disease activity (LDA), OR=1.45, 95% CI=1.08 to 1.94; moderate/high disease activity (M/HDA), OR=1.37, 95% CI=0.97 to 1.95; vs remission), and cessation/reduction of antirheumatic medication before or after vaccination (OR=4.76, 95% CI=3.44 to 6.58); factors associated with decreased odds of flare were: higher age (OR=0.90, 95% CI=0.83 to 0.98), non-Pfizer/AstraZeneca/Moderna vaccines (OR=0.10, 95% CI=0.01 to 0.74; vs Pfizer), and exposure to methotrexate (OR=0.57, 95% CI=0.37 to 0.90), tumour necrosis factor inhibitors (OR=0.55, 95% CI=0.36 to 0.85) or rituximab (OR=0.27, 95% CI=0.11 to 0.66), versus no antirheumatic treatment. In a multivariable model using new medication or dosage increase due to flare as the dependent variable, only the following independent associations were observed: active disease (LDA, OR=1.47, 95% CI=0.94 to 2.29; M/HDA, OR=3.08, 95% CI=1.91 to 4.97; vs remission), cessation/reduction of antirheumatic medication before or after vaccination (OR=2.24, 95% CI=1.33 to 3.78),

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Post-SARS-CoV-2 vaccination disease flares are not frequent in people with inflammatory/autoimmune rheumatic and musculoskeletal diseases (I-RMDs).

⇒ Previous studies have been smaller and mainly analysed patient-reported flares, with flare rates typically higher compared with physician-reported flares, often failing to distinguish I-RMD flares from short-term vaccine reactogenicity.

WHAT THIS STUDY ADDS

⇒ In this large international physician-reported registry, I-RMD flares and flares requiring medication following vaccination against SARS-CoV-2 were infrequent (3.7 and 1.6%, respectively).

⇒ Higher disease activity at the time of SARS-CoV-2 vaccination and cessation/reduction of antirheumatic medications before or after vaccination were associated with an increased probability of flare, while exposure to certain medications such as methotrexate and rituximab was associated with a decreased probability of flare.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These data will aid patients, clinicians and other healthcare professionals making shared informed decisions regarding I-RMD management in the context of vaccination.

⇒ These findings will help to inform vaccination strategies in patients with I-RMDs, specifically decisions regarding stopping or reducing antirheumatic medications around the time of vaccination.

and exposure to methotrexate (OR=0.48, 95% CI=0.26 to 0.89) or rituximab (OR=0.10, 95% CI=0.01 to 0.77), versus no antirheumatic treatment.

Conclusion I-RMD flares following SARS-CoV-2 vaccination were uncommon. Factors associated with flares were identified, namely higher disease activity and cessation/reduction of antirheumatic medications before or after vaccination.

INTRODUCTION

The COVID-19 pandemic caused unprecedented pressure on healthcare systems and resulted in a dramatic loss of human life worldwide.[1 2] The development of highly effective vaccines against SARS-CoV-2 changed the course of the pandemic, with many lives saved by immunisation against SARS-CoV-2, including the lives of patients with inflammatory/autoimmune rheumatic and musculoskeletal diseases (I-RMDs).[3–10]

Using early data from the international observational European Alliance of Associations for Rheumatology (EULAR) Coronavirus Vaccine (COVAX) physician-reported registry, we previously reported that COVID-19 vaccines were well tolerated by patients with I-RMD with infrequent reports of I-RMD flare (4.4%, 1.5% requiring medication changes) and very infrequent reports of serious adverse events (AEs) (0.4%).[8] Other studies have mainly analysed patient-reported flares, with flare rates typically being higher compared with physician-reported flares, and often failing to distinguish I-RMD flares from short-term vaccine reactogenicity.[11–23]

The possibility of I-RMD flares has raised concerns, not only because there might be specific demographic or clinical features associated with increased risk of post-vaccination flare, but also because some organisations have recommended conventional and targeted synthetic disease-modifying antirheumatic drugs (cs/tsDMARDs) to be withheld 'for 1–2 weeks (as disease activity allows) after each COVID-19 vaccine dose', a strategy that could contribute to increased frequency of post-vaccination I-RMD flares.[24]

Our aim was to investigate the frequency and factors associated with I-RMD flare following vaccination against SARS-CoV-2 in people with I-RMD.

METHODS

Data collection

The EULAR COVAX physician-reported registry (https://www.eular.org/eular-covax-registry)[8] was an observational registry of patients with a pre-existing I-RMD or non-I-RMD who received one or more doses of any vaccine against SARS-CoV-2. The registry was launched in February 2021 and closed in October 2022. Data were recorded voluntarily by rheumatologists or other members of the clinical rheumatology team directly into an online data entry system (using REDCap,[25 26] which is a secure web application for building and managing online surveys and databases) or transferred from a national registry (for Portugal). Cases included in this study had a pre-existing I-RMD diagnosis and received one or two doses of the same COVID-19 vaccine. Patients receiving a combination of vaccines were excluded. Patients receiving more than two doses of the same vaccine were also excluded because disease activity data were only collected at baseline (ie, at the time of first dose of primary vaccination schedule).

Data collected included patients' age (years), sex, country of residence, primary I-RMD diagnosis, COVID-19 vaccine received, number of doses and dates, physician global assessment of disease activity at the time of first dose of primary vaccination schedule (categorised as remission, low, moderate or high disease activity), exposure to immunomodulatory/immunosuppressive treatments at the time of vaccination, cessation/reduction of antirheumatic medication before or after vaccination, development of post-vaccination I-RMD flares and their characteristics, and prescription of new antirheumatic medication or dosage increase due to flare.

Providers were asked to report as many cases as possible of patients with RMDs vaccinated against SARS-CoV-2, with or without flares. 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, to avoid selection bias. Furthermore, the time from vaccination to the reporting of the case/outcome/flare was allowed to vary between individuals. Providers were also asked to distinguish between I-RMD flares and AEs, namely AEs within 7 days from vaccination (reactogenicity) and AEs of special interest.

Diagnostic groups

Diagnostic groups were defined based on the physician-reported primary I-RMD diagnosis: (1) inflammatory joint diseases (IJD), (2) connective tissue diseases (CTDs), (3) vasculitis and (4) other I-RMDs. Rheumatic diseases included in each category are listed in table 1.

Antirheumatic medications

Exposure to the following immunomodulatory/immunosuppressive treatments at the time of COVID-19 vaccination was gathered: (1) csDMARDs: antimalarials (hydroxychloroquine and chloroquine), leflunomide, methotrexate and sulfasalazine; (2) biological DMARDs (bDMARDs): abatacept, belimumab, rituximab, interleukin (IL)-1 inhibitors (anakinra, canakinumab and rilonacept), IL-6 inhibitors (tocilizumab, sarilumab), IL-12/23 inhibitors (ustekinumab), IL-23 inhibitors (guselkumab, risankizumab and tildrakizumab), IL-17 inhibitors (secukinumab, ixekizumab and brodalumab) and tumour necrosis factor (TNF) inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab and TNF inhibitor biosimilars); (3) tsDMARDs: apremilast and Janus kinase (JAK) inhibitors (tofacitinib, baricitinib and upadacitinib); (4) immunosuppressants: glucocorticoids, azathioprine/6-mercaptopurine, cyclophosphamide, ciclosporin, mycophenolate mofetil and tacrolimus; (5) other drugs, including intravenous immunoglobulin and antifibrotics.

I-RMD flare characteristics and definition

Flare was defined by physician report (signs and symptoms interpreted by the local physician as being suggestive of post-vaccination I-RMD flare). The following detailed information about flares was collected: (1) type of flare (including 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 types of flare); (2) severity of flare (mild, moderate, severe without hospitalisation and severe with hospitalisation); (3) information about changes in antirheumatic medication (including dosage increase or new medication) due to the flare; and (4) period of time between vaccination and the flare.

Statistical analyses

Data were reported descriptively for the entire cohort of patients with I-RMDs and for each diagnostic group. Factors associated

Table 1 Patients' demographics and clinical characteristics

		IJD n=5207 (71%)	CTD n=1320 (18%)	Vasculitis n=686 (9.4%)	OIRMD n=123 (1.7%)	All patients n=7336
Age, years	Mean (SD)	58.2 (15)	54.5 (15.9)	67.7 (15.1)	53.3 (13.7)	58.3 (15.5)
	Range	18–96	18–90	19–95	18–87	18–96
Sex	Female	3356 (64.5)	1153 (87.3)	407 (59.3)	67 (54.5)	4983 (67.9)
	Male	1851 (35.5)	167 (12.7)	279 (40.7)	56 (45.5)	2353 (32.1)
Country	Portugal	1892 (36.3)	341 (25.8)	21 (3.1)	1 (0.8)	2255 (30.7)
	France	1095 (21)	489 (37)	326 (47.5)	67 (54.5)	1977 (26.9)
	Italy	716 (13.8)	219 (16.6)	136 (19.8)	28 (22.8)	1099 (15)
	Slovakia	348 (6.7)	45 (3.4)	36 (5.2)	0	429 (5.8)
	Latvia	284 (5.5)	47 (3.6)	20 (2.9)	0	351 (4.8)
	Other countries*	872 (16.7)	179 (13.6)	147 (21.4)	27 (22)	1225 (16.7)
Primary I-RMD diagnosis	Rheumatoid arthritis	2647 (50.1)	NA	NA	NA	2647 (36.1)
	Axial spondyloarthritis	1184 (22.7)	NA	NA	NA	1184 (16.1)
	Psoriatic arthritis	892 (17.1)	NA	NA	NA	892 (12.2)
	Other peripheral spondyloarthritis (including reactive arthritis)	178 (3.4)	NA	NA	NA	178 (2.4)
	Non-systemic juvenile idiopathic arthritis	88 (1.7)	NA	NA	NA	88 (1.2)
	Systemic juvenile idiopathic arthritis	14 (<1)	NA	NA	NA	14 (<1)
	Gout or other crystal arthritis	100 (1.9)	NA	NA	NA	100 (1.4)
	Other inflammatory arthritis	104 (2)	NA	NA	NA	104 (1.4)
	Systemic lupus erythematosus	NA	546 (41.4)	NA	NA	546 (7.4)
	Primary antiphospholipid syndrome	NA	33 (2.5)	NA	NA	33 (<1)
	Sjogren's syndrome	NA	294 (22.3)	NA	NA	294 (4)
	Systemic sclerosis	NA	245 (18.6)	NA	NA	245 (3.3)
	Idiopathic inflammatory myopathy	NA	86 (6.5)	NA	NA	86 (1.2)
	Mixed connective tissue disease	NA	44 (3.3)	NA	NA	44 (<1)
	Undifferentiated connective tissue disease	NA	72 (5.5)	NA	NA	72 (1)
	Large vessel vasculitis—Takayasu arteritis	NA	NA	18 (2.6)	NA	18 (<1)
	Large vessel vasculitis—giant cell arteritis	NA	NA	157 (22.9)	NA	157 (2.1)
	Polymyalgia rheumatica	NA	NA	270 (39.4)	NA	270 (3.7)
	Medium vessel vasculitis—polyarteritis nodosa, Kawasaki disease	NA	NA	14 (2)	NA	14 (<1)
	ANCA-associated vasculitis—MPA, GPA, EGPA	NA	NA	139 (20.3)	NA	139 (1.9)
	Immune complex small vessel vasculitis	NA	NA	9 (1.3)	NA	9 (<1)
	Bechet's disease	NA	NA	50 (7.3)	NA	50 (<1)
	Other vasculitis	NA	NA	29 (4.2)	NA	29 (<1)
	Monogenic autoinflammatory syndrome	NA	NA	NA	17 (13.8)	17 (<1)
	Non-monogenic autoinflammatory syndrome	NA	NA	NA	15 (12.2)	15 (<1)
	IgG_4-related disease	NA	NA	NA	16 (13)	16 (<1)
	Sarcoidosis	NA	NA	NA	63 (51.2)	63 (<1)
	Relapsing polychondritis	NA	NA	NA	9 (7.3)	9 (<1)
	Chronic recurrent multifocal osteomyelitis	NA	NA	NA	3 (2.4)	3 (<1)

*Other countries include Albania, Australia, Austria, Belgium, Croatia, Czechia, Estonia, Germany, Greece, Hungary, Ireland, Lithuania, Luxembourg, Monaco, Netherlands, Poland, Republic of Moldova, Romania, Russian Federation, Slovenia, Spain, Switzerland, Turkey, Ukraine, USA and UK.
ANCA, antineutrophil cytoplasmic antibody; CTD, connective tissue disease; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; IJD, inflammatory joint disease; I-RMD, inflammatory rheumatic and musculoskeletal disease; MPA, microscopic polyangiitis; NA, not applicable; OIRMD, other inflammatory rheumatic and musculoskeletal disease.

with COVID-19 vaccination-related disease flares were estimated using univariable and multivariable logistic regression analyses and reported as OR and 95% CI. Two separate multivariable models were built, one with 'I-RMD flare' as dependent variable and one with 'new antirheumatic medication or dosage increase due to flare' as dependent variable.

Covariates included in the models were the following: age (per decade of life), sex, rheumatic disease diagnostic group (IJD (reference), CTD, vasculitis and other inflammatory rheumatic diseases), disease activity (remission (reference), low disease activity, and moderate or high disease activity), vaccine type (Pfizer/BioNTech (reference), Moderna, AstraZeneca and other vaccines), rheumatic disease treatment and cessation/reduction of antirheumatic medications at the time of vaccination.

For patients being treated with more than one of the medications of interest (except glucocorticoids), we created a medication hierarchy based on clinical expertise to categorise patients, as previously reported.[10] This process creates disjoint categories, allowing a clear reference group for interpretation of the regression models and avoiding collinearities. The following hierarchy of treatment allocation was used: immunosuppressants (azathioprine/6-mercaptopurine, cyclophosphamide,

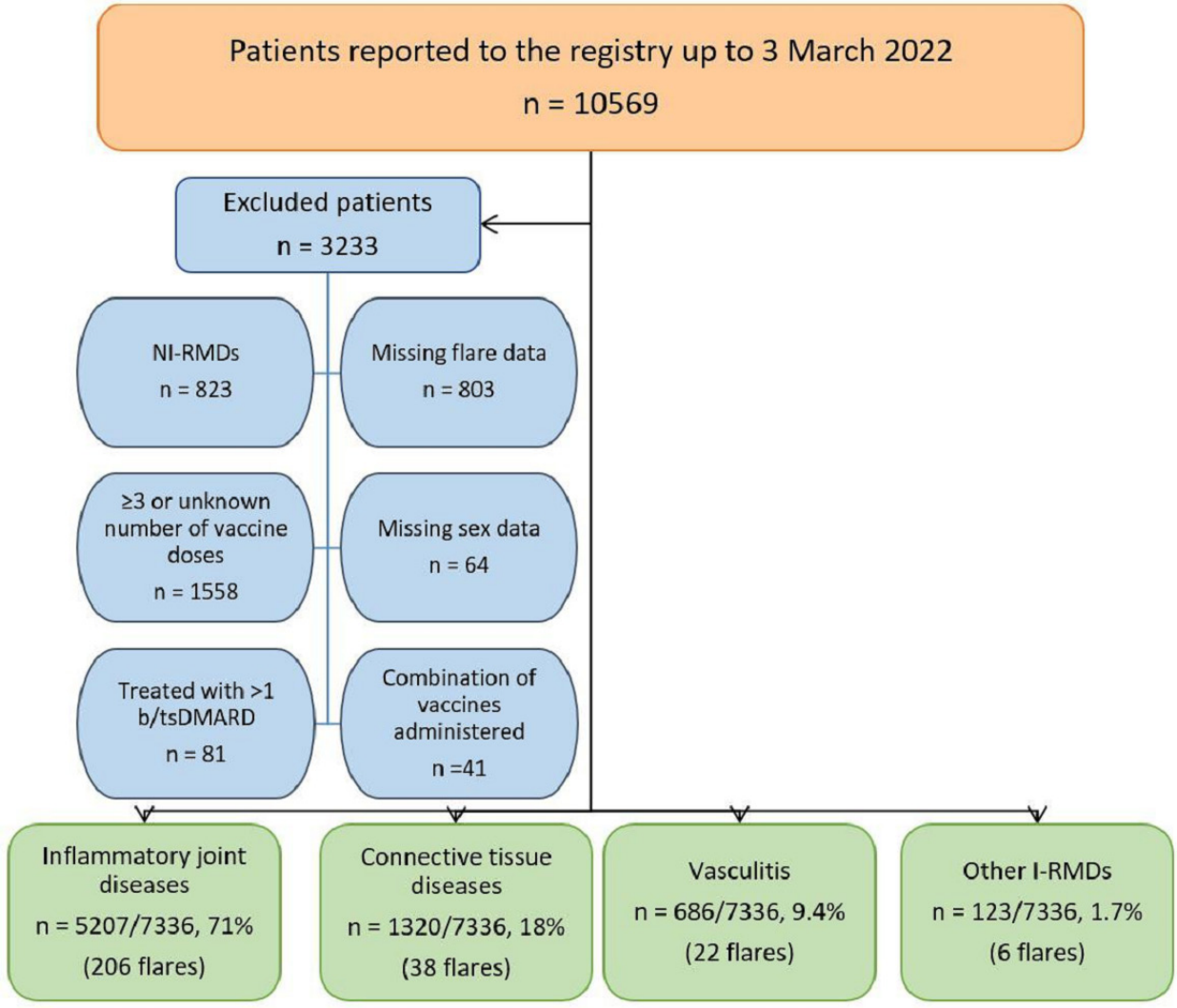

Figure 1 Study flow chart. Some patients were excluded for more than one reason. bDMARD, biological disease-modifying antirheumatic drug; I-RMDs, inflammatory rheumatic and musculoskeletal diseases; NI-RMD, non-inflammatory rheumatic and musculoskeletal disease; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

ciclosporin, mycophenolate mofetil and tacrolimus)>methotrexate>leflunomide>sulfasalazine>antimalarials. Patients receiving b/tsDMARDs were considered solely in the b/tsDMARD group. Glucocorticoids were analysed separately in the model.

Missing values for vaccine type and disease activity were derived by multiple imputation using full conditional specification (age, sex, flare, country of residence, disease group, disease activity, vaccine type and exposure to glucocorticoid treatment were included in the imputation model). Results of the logistic regression analyses for 100 imputed datasets were pooled by Rubin's rules. Secondary models (sensitivity analysis) were performed without data imputation.

RESULTS

General characteristics

Of 10 569 patients reported to the registry, 7336 patients with I-RMDs were included in this study. Reasons for exclusion are presented in figure 1. The majority were female (68%) and mean age was 58.3 (SD 15.5) years. Most patients had IJD (71%), followed by CTD (18%), vasculitis (9.4%) and other I-RMDs (1.7%). Three-quarters of the diagnoses consisted of rheumatoid arthritis (RA; 36.1%), axial spondyloarthritis (axSpA; 16.1%), psoriatic arthritis (PsA; 12.2%), systemic lupus erythematosus (SLE; 7.4%) and polymyalgia rheumatica (PMR; 3.7%) (table 1).

While the majority of patients were in remission (39.7%) or had low disease activity (27.4%), 17.8% of all cases had missing data on disease activity, and the remaining patients (15.1%) had moderate or high disease activity. The most frequently used medication groups were csDMARDs (58.2%), ts/bDMARDs (49%) and immunosuppressants (35.2%), respectively. The rate of not using antirheumatic medications was 7% (table 2). The most common individual medications were methotrexate (34.1%), glucocorticoids (30.3%) and TNF inhibitors (30.3%). In terms of disease subgroups, the use of csDMARDs and b/tsDMARDs was highest in IJD (63.2% and 63%, respectively), while the use of immunosuppressants was highest in vasculitis (72.2%).

In terms of vaccination, 17.7% of the included cases received one dose, while 82.3% received two doses (table 3). Among those who received two doses, the majority received the Pfizer/BioNTech vaccine (74.1%), followed by the AstraZeneca (13.2%) and Moderna vaccines (9.4%). Similarly, among patients who received only one dose, the Pfizer/

Table 2 Inflammatory/autoimmune rheumatic and musculoskeletal disease activity and medications

	IJD n=5207	CTD n=1320	Vasculitis n=686	OIRMD n=123	All patients n=7336
Physician-reported disease activity					
Remission	1934 (37.1)	526 39.8)	393 (57.3)	62 (50.4)	2915 (39.7)
Low disease activity	1487 (28.6)	304 (23)	180 (26.2)	40 (32.5)	2011 (27.4)
Moderate disease activity	808 (15.5)	74 (5.6)	47 (6.9)	9 (7.3)	938 (12.8)
High disease activity	147 (2.8)	12 (0.9)	8 (1.2)	1 (0.8)	168 (2.3)
Missing/unknown	831 (16)	404 (30.6)	58 (8.4)	11 (9)	1304 (17.8)
Antirheumatic medication exposure					
csDMARDs	3289 (63.2)	786 (59.6)	163 (23.8)	31 (25.2)	4269 (58.2)
Antimalarials	323 (6.2)	632 (47.9)	11 (1.6)	8 (6.5)	974 (13.3)
Held before vaccination	1	1	0	0	2
Reduced before vaccination	0	1	0	0	1
Held after vaccination	1	2	0	0	3
Reduced after vaccination	0	2	0	0	2
Leflunomide	379 (7.3)	14 (1.1)	9 (1.3)	1 (<1)	403 (5.5)
Held before vaccination	6	0	0	0	6
Reduced before vaccination	1	0	0	0	1
Held after vaccination	2	0	0	0	2
Reduced after vaccination	0	0	0	0	0
Methotrexate	2200 (42.3)	139 (10.5)	141 (20.6)	22 (17.9)	2502 (34.1)
Held before vaccination	66	3	5	0	74
Reduced before vaccination	10	0	1	0	11
Held after vaccination	137	6	7	1	151
Reduced after vaccination	6	0	0	0	6
Sulfasalazine	387 (7.4)	1 (<1)	2 (<1)	0	390 (5.3)
Held before vaccination	1	0	0	0	1
Reduced before vaccination	0	0	0	0	0
Held after vaccination	0	0	0	0	0
Reduced after vaccination	1	0	0	0	1
bDMARDs	3042 (58.4)	130 (9.8)	146 (21.3)	31 (25.2)	3349 (45.7)
Abatacept	118 (2.3)	2 (<1)	1 (<1)	0	121 (1.6)
Held before vaccination	6	0	0	0	6
Reduced before vaccination	0	0	0	0	0
Held after vaccination	3	0	0	0	3
Reduced after vaccination	0	0	0	0	0
Belimumab	0	38 (2.9)	0	0	38 (<1)
Held before vaccination	0	2	0	0	2
Reduced before vaccination	0	0	0	0	0
Held after vaccination	0	0	0	0	0
Reduced after vaccination	0	0	0	0	0
Rituximab	187 (3.6)	71 (5.4)	57 (8.3)	6 (4.9)	321 (4.4)
Held before vaccination	14	1	7	2	24
Reduced before vaccination	1	0	0	1	2
Held after vaccination	1	1	0	0	2
Reduced after vaccination	1	0	0	0	1
IL-1 inhibitors	19 (<1)	2 (<1)	1 (<1)	7 (5.7)	29 (<1)
Held before vaccination	0	0	0	0	0
Reduced before vaccination	0	0	0	0	0
Held after vaccination	0	0	0	0	0
Reduced after vaccination	0	0	0	0	0
IL-6 inhibitors	278 (5.3)	9 (<1)	63 (9.2)	3 (2.4)	353 (4.8)
Held before vaccination	13	1	3	0	17
Reduced before vaccination	0	0	0	0	0
Held after vaccination	9	0	0	0	9
Reduced after vaccination	1	0	0	0	1
IL-12/23 inhibitors	46 (<1)	2 (<1)	1 (<1)	0	49 (<1)
Held before vaccination	1	0	1	0	2
Reduced before vaccination	0	0	0	0	0
Held after vaccination	0	0	0	0	0
Reduced after vaccination	0	0	0	0	0
IL-23 inhibitors	6 (<1)	0	0	0	6 (<1)
Held before vaccination	0	0	0	0	0
Reduced before vaccination	0	0	0	0	0

Continued

Table 2 Continued

	IJD n=5207	CTD n=1320	Vasculitis n=686	OIRMD n=123	All patients n=7336
Held after vaccination	0	0	0	0	0
Reduced after vaccination	0	0	0	0	0
IL-17 inhibitors	207 (4.2)	1 (<1)	0	1 (<1)	209 (2.8)
Held before vaccination	5	0	0	0	5
Reduced before vaccination	0	0	0	0	0
Held after vaccination	5	0	0	0	5
Reduced after vaccination	1	0	0	0	1
TNF inhibitors	2181 (41.9)	5 (<1)	23 (3.4)	14 (11.4)	2223 (30.3)
Held before vaccination	67	0	2	0	69
Reduced before vaccination	9	0	0	0	9
Held after vaccination	58	1	1	0	60
Reduced after vaccination	5	0	0	0	5
tsDMARDs	241 (4.6)	7 (<1)	1 (<1)	0	249 (3.4)
Apremilast	13 (<1)	0	0	0	13 (<1)
Held before vaccination	0	0	0	0	0
Reduced before vaccination	0	0	0	0	0
Held after vaccination	0	0	0	0	0
Reduced after vaccination	0	0	0	0	0
JAK inhibitors	228 (4.4)	7 (<1)	1 (<1)	0	236 (3.2)
Held before vaccination	7	0	0	0	7
Reduced before vaccination	2	0	0	0	2
Held after vaccination	26	1	0	0	27
Reduced after vaccination	2	0	0	0	2
Immunosuppressants	1294 (24.9)	729 (55.2)	495 (72.2)	63 (51.2)	2581 (35.2)
Glucocorticoids (systemic)	1255 (24.1)	463 (35.1)	447 (65.2)	56 (45.5)	2221 (30.3)
Held before vaccination	2	2	2	0	6
Reduced before vaccination	3	1	2	0	6
Held after vaccination	4	0	2	0	6
Reduced after vaccination	1	0	7	0	8
Azathioprine/6-mercaptopurine	19 (<1)	94 (7.1)	32 (4.7)	4 (3.3)	149 (2)
Held before vaccination	0	2	0	1	3
Reduced before vaccination	0	0	0	0	0
Held after vaccination	0	1	0	0	1
Reduced after vaccination	0	0	0	0	0
Ciclosporin	12 (<1)	17 (1.3)	0	0	29 (<1)
Held before vaccination	1	1	0	0	2
Reduced before vaccination	0	0	0	0	0
Held after vaccination	0	0	0	0	0
Reduced after vaccination	0	0	0	0	0
Cyclophosphamide	1 (<1)	7 (<1)	5 (<1)	0	13 (<1)
Held before vaccination	0	0	0	0	0
Reduced before vaccination	0	0	0	0	0
Held after vaccination	0	0	0	0	0
Reduced after vaccination	0	0	0	0	0
Mycophenolate mofetil/mycophenolic acid	5 (<1)	142 (10.8)	11 (1.6)	3 (2.4)	161 (2.2)
Held before vaccination	1	4	0	0	5
Reduced before vaccination	0	0	0	0	0
Held after vaccination	0	3	0	0	3
Reduced after vaccination	0	1	0	0	1
Tacrolimus	2 (<1)	6 (<1)	0	0	8 (<1)
Held before vaccination	0	0	0	0	0
Reduced before vaccination	0	0	0	0	0
Held after vaccination	0	0	0	0	0
Reduced after vaccination	0	0	0	0	0
Other medications					
Intravenous immunoglobulin	1 (<1)	12 (<1)	2 (<1)	1 (<1)	16 (<1)
Held before vaccination	0	0	0	0	0
Reduced before vaccination	0	0	0	0	0
Held after vaccination	0	1	0	0	1
Reduced after vaccination	0	0	0	0	0
Antifibrotics	8 (<1)	2 (<1)	0	0	10 (<1)
Held before vaccination	0	0	0	0	0

Continued

Table 2 Continued

	IJD n=5207	CTD n=1320	Vasculitis n=686	OIRMD n=123	All patients n=7336
Reduced before vaccination	0	0	0	0	0
Held after vaccination	0	0	0	0	0
Reduced after vaccination	0	0	0	0	0
No DMARD therapy	201 (3.9)	224 (17)	71 (10.3)	20 (16.3)	516 (7)
Unknown	46 (<1)	37 (2.8)	3 (<1)	1 (<1)	87 (1.2)

All medications including monotherapy and/or combination therapy.
bDMARDs, biological DMARDs; csDMARDs, conventional synthetic DMARDs; CTD, connective tissue disease; DMARD, disease-modifying antirheumatic drug; IJD, inflammatory joint disease; IL, interleukin; JAK, Janus kinase; OIRMD, other inflammatory rheumatic and musculoskeletal disease; TNF, tumour necrosis factor; tsDMARDs, targeted synthetic DMARDs.

BioNTech, AstraZeneca and Moderna vaccines were also the most commonly administered, accounting for 42.8%, 9.2% and 30.8% of cases, respectively.

Demographic and clinical characteristics of patients with post-vaccination I-RMD flare

Disease flares were reported in 272 (3.7%) of the 7336 patients. Of these patients, 206 (4%) were in the IJD group, 38 (2.9%) in the CTD group, 22 (3.2%) in the vasculitis group and 6 (4.9%) in the other I-RMD group. Mean age of patients with post-vaccination flare was 56.2 (SD 14.3) years and most patients were female (204 of 272, 75%). Most patients had low disease activity (37.9%) before vaccination, followed by remission (36%), moderate (18.8) and high disease activity (1.5%). The most recent vaccine dose before flare was the first in 38.6% and the second in 36% of patients, although these data were missing in 25% of cases. Mean time between flare and the most recent vaccine dose was 7.2 days (SD 8.2). Mean time between vaccination and case reporting was 115 days (SD 98). Most flares were mild (34.2%) or moderate (45.6%), although severe flares with or without hospitalisation occurred in 4.4% and 9.2% of the flare cases, respectively. Flare of arthritis (49.6%), polyarthralgia (37.9%) and increase in fatigue (12.1%) were the most common types of flare. In addition, 44.5% of patients with a flare (1.6% of all patients) started on a new medication or increased the dosage of an existing medication because of the flare (table 4 and online supplemental table 1). TNF inhibitors (30.5), methotrexate (30.1%) and glucocorticoids (24.6%) were the most commonly used drugs, when a flare was observed (online supplemental table 2).

Factors associated with I-RMD flare

In univariable analyses, the following variables were found to be associated with I-RMD flare: age, female sex, low disease activity (vs remission), other vaccine types (vs Pfizer/AstraZeneca/Moderna vaccines) and cessation/reduction of antirheumatic medications at the time of vaccination. Furthermore, moderate/high disease activity (vs remission), exposure to methotrexate, exposure to rituximab and cessation/reduction of antirheumatic medications at the time of vaccination were associated with new medication or dosage increase due to flare (online supplemental table 3).

Two separate multivariable models were built, one with 'I-RMD flare' as dependent variable and one with 'new medication or dosage increase due to flare' as dependent variable (table 5).

Independent factors associated with I-RMD flare were: higher age (per decade of life: OR=0.90, 95% CI=0.83 to 0.98), female sex (OR=1.40, 95% CI=1.05 to 1.87), active disease (low disease activity, OR=1.45, 95% CI=1.08 to 1.94; moderate/high disease activity, OR=1.37, 95% CI=0.97 to 1.95; vs remission), non-Pfizer/AstraZeneca/Moderna vaccines (OR=0.10, 95% CI=0.01 to 0.74; vs Pfizer), cessation/reduction of antirheumatic medication before or after vaccination (OR=4.76, 95% CI=3.44 to 6.58), and exposure to methotrexate (OR=0.57, 95% CI=0.37 to 0.90), TNF inhibitors (OR=0.55, 95% CI=0.36 to 0.85) and rituximab (OR=0.27, 95% CI=0.11 to 0.66), compared with no antirheumatic treatment.

In the multivariable model with new medication or dosage increase due to flare as the dependent variable, the only independent associations observed were: active disease (low disease

Table 3 SARS-CoV-2 vaccination and flares in patients with inflammatory/autoimmune rheumatic and musculoskeletal diseases

	IJD n=5207	CTD n=1320	Vasculitis n=686	OIRMD n=123	All patients n=7336
Vaccine administered					
Pfizer	3446 (66.2)	973 (73.7)	517 (75.4)	93 (75.6)	5029 (68.6)
Moderna	508 (9.8)	118 (8.9)	63 (9.2)	6 (4.9)	695 (9.5)
AstraZeneca	934 (17.9)	158 (12)	94 (13.7)	14 (11.4)	1200 (16.4)
Janssen	154 (3)	25 (1.9)	4 (0.6)	0	183 (2.5)
Sputnik V	6 (0.1)	1 (0.1)	0	0	7 (0.1)
CoronaVac/Sinovac	31 (0.6)	22 (1.7)	6 (0.9)	10 (8.1)	69 (0.9)
Other	3 (0.1)	0	1 (0.1)	0	4 (0.1)
Number of doses administered					
One	935 (18)	229 (17.3)	121 (17.6)	15 (12.2)	1300 (17.7)
Two	4272 (82)	1091 (82.7)	565 (82.4)	108 (87.8)	6036 (82.3)
Flare following vaccination					
Yes	206 (4)	38 (2.9)	22 (3.2)	6 (4.9)	272 (3.7)
No	5001 (96)	1282 (97.1)	664 (96.8)	117 (95.1)	7064 (96.3)

CTD, connective tissue disease; IJD, inflammatory joint disease; OIRMD, other inflammatory rheumatic and musculoskeletal disease.

Table 4 Demographic and clinical characteristics of patients with post-vaccination flare

	IJD n=206	CTD n=38	Vasculitis n=22	OIRMD n=6	All patients n=272
Age, years, mean (SD)	56.2 (13.4)	50.8 (13.1)	66.6 (18.9)	53.7 (17.7)	56.2 (14.3)
Sex					
Female	156 (75.7)	32 (84.2)	14 (63.6)	2 (33.3)	204 (75)
Male	50 (24.3)	6 (15.8)	8 (36.4)	4 (66.7)	68 (25)
Disease activity					
Remission	69 (33.5)	15 (39.5)	13 (59.1)	1 (16.7)	98 (36)
Low disease activity	86 (41.7)	10 (26.3)	5 (22.7)	2 (33.3)	103 (37.9)
Moderate disease activity	36 (17.5)	8 (21.1)	4 (18.2)	3 (50)	51 (18.8)
High disease activity	4 (1.9)	0	0	0	4 (1.5)
Missing/unknown	11 (5.4)	5 (13.1)	0	0	16 (5.9)
Vaccine dose before flare					
First	80 (38.8)	13 (34.2)	8 (36.4)	4 (66.7)	105 (38.6)
Second	73 (35.4)	15 (39.5)	9 (40.9)	1 (16.7)	98 (36)
Unknown/missing	53 (25.7)	10 (26.3)	5 (22.7)	1 (16.7)	69 (25)
Vaccine type before flare					
Pfizer	140 (68)	29 (76.3)	18 (81.8)	4 (66.7)	191 (70.2)
Moderna	20 (9.7)	3 (7.9)	0	1 (16.7)	24 (8.8)
AstraZeneca	43 (20.9)	6 (15.8)	4 (18.2)	0	53 (19.5)
CoronaVac/Sinovac	0	0	0	1 (16.7)	1 (0.4)
Unknown/missing	3 (1.5)	0	0	0	3 (1.1)
Time between vaccine and flare, days, mean (SD)	6.8 (7.9) (n=141)	7.8 (7.5) (n=27)	11.1 (11.4) (n=16)	1 (1) (n=3)	7.2 (8.2) (n=187)
Type of flare					
Fever	15 (7.3)	4 (10.5)	2 (9.1)	1 (16.7)	22 (8.1)
Weight loss	0	0	0	1 (16.7)	1 (0.4)
Increase in fatigue	16 (7.8)	10 (26.3)	4 (18.2)	3 (50)	33 (12.1)
Increase in dryness	0	3 (7.9)	0	1 (16.7)	4 (1.5)
Enlarged lymph nodes	2 (1)	3 (7.9)	0	0	5 (1.8)
Polyarthralgia	77 (37.4)	14 (36.8)	9 (40.9)	3 (50)	103 (37.9)
Arthritis flare	118 (57.3)	9 (23.7)	7 (31.8)	1 (16.7)	135 (49.6)
Cutaneous flare	9 (4.4)	6 (15.8)	2 (9.1)	3 (50)	20 (7.4)
Pulmonary flare	1 (0.5)	1 (2.6)	2 (9.1)	0	4 (1.5)
Renal flare	0	0	2 (9.1)	0	2 (0.7)
Neurological flare	0	2 (5.3)	1 (4.5)	0	3 (1.1)
Muscular flare	6 (2.9)	4 (10.5)	3 (13.6)	1 (16.7)	14 (5.1)
Cardiac flare	1 (0.5)	1 (2.6)	1 (4.5)	0	3 (1.1)
Gastrointestinal flare	1 (0.5)	0	0	0	1 (0.4)
Haematological flare	0	3 (7.9)	0	0	3 (1.1)
Other	16 (7.8)	3 (7.9)	1 (4.5)	2 (33.3)	22 (8.1)
Severity of flare					
Mild	69 (33.5)	17 (44.7)	6 (27.3)	1 (16.7)	93 (34.2)
Moderate	101 (49)	12 (31.6)	10 (45.5)	1 (16.7)	124 (45.6)
Severe without hospitalisation	19 (9.2)	2 (5.3)	3 (13.6)	1 (16.7)	25 (9.2)
Severe with hospitalisation	2 (1)	4 (10.5)	3 (13.6)	3 (50)	12 (4.4)
Unknown	8 (3.9)	2 (5.3)	0	0	10 (3.7)
New medication or dosage increase due to flare					
Yes	86 (41.7)	19 (50)	13 (59.1)	3 (50)	121 (44.5)
No	110 (53.4)	15 (39.5)	8 (36.4)	3 (50)	136 (50)
Unknown	10 (4.9)	4 (10.5)	1 (4.5)	0	15 (5.5)

CTD, connective tissue disease; IJD, inflammatory joint disease; OIRMD, other inflammatory rheumatic and musculoskeletal disease.

activity, OR=1.47, 95% CI=0.94 to 2.29; moderate/high disease activity, OR=3.08, 95% CI=1.91 to 4.97; vs remission), cessation/reduction of antirheumatic medication before or after vaccination (OR=2.24, 95% CI=1.33 to 3.78), and exposure to methotrexate (OR=0.48, 95% CI=0.26 to 0.89) and rituximab (OR=0.10, 95% CI=0.01 to 0.77), compared with no antirheumatic treatment.

Secondary models (sensitivity analysis) performed without data imputation yield very similar results to the primary analysis (online supplemental table 4).

DISCUSSION

The EULAR COVAX physician-reported registry represents the largest international case series of individuals with I-RMDs who received vaccination against SARS-CoV-2. Within this study, flares were reported in 3.7% of patients with I-RMD, while flares requiring starting a new medication or increasing the dosage of an existing medication were reported in 1.6% of the patients. Higher disease activity and cessation/reduction of antirheumatic medications before or after vaccination were associated with an increased probability of flare, while exposure to certain

Table 5 Multivariable logistic regression analysis of factors associated with flare, using either 'I-RMD flare' or 'new antirheumatic medication or dosage increase due to flare' as the dependent variable

Covariates	Outcome: flare		Outcome: new medication or dosage increase due to flare	
	OR (95% CI)	P value	OR (95% CI)	P value
Age, per decade of life	0.90 (0.83 to 0.98)	0.015	0.92 (0.81 to 1.04)	0.18
Female sex	1.40 (1.05 to 1.87)	0.021	1.24 (0.82 to 1.88)	0.31
Diagnostic group				
Inflammatory joint diseases	Reference		Reference	
Connective tissue diseases	0.68 (0.43 to 1.08)	0.10	0.84 (0.45 to 1.57)	0.59
Vasculitis	0.96 (0.57 to 1.62)	0.88	0.93 (0.47 to 1.85)	0.84
Other I-RMD	1.34 (0.56 to 3.21)	0.51	1.09 (0.32 to 3.70)	0.89
Disease activity				
Remission	Reference		Reference	
Low disease activity	1.45 (1.08 to 1.94)	0.013	1.47 (0.94 to 2.29)	0.093
Moderate/high disease activity	1.37 (0.97 to 1.95)	0.075	3.08 (1.91 to 4.97)	<0.001
Vaccine				
Pfizer	Reference		Reference	
Moderna	0.87 (0.56 to 1.34)	0.52	1.37 (0.77 to 2.45)	0.29
AstraZeneca	1.13 (0.83 to 1.56)	0.44	1.41 (0.90 to 2.22)	0.13
Other	0.10 (0.01 to 0.74)	0.023	0	1
Antirheumatic medication				
None	Reference		Reference	
Immunosuppressants	0.32 (0.07 to 1.35)	0.12	0	1
Methotrexate	0.57 (0.37 to 0.90)	0.014	0.48 (0.26 to 0.89)	0.019
Leflunomide	1.24 (0.60 to 2.57)	0.57	0.76 (0.25 to 2.25)	0.62
Sulfasalazine	0.85 (0.35 to 2.07)	0.71	0.75 (0.22 to 2.62)	0.65
Antimalarials	0.78 (0.43 to 1.40)	0.41	0.47 (0.19 to 1.18)	0.11
TNFi	0.55 (0.36 to 0.85)	0.007	0.60 (0.33 to 1.09)	0.096
tsDMARDs	0.56 (0.28 to 1.13)	0.11	0.39 (0.13 to 1.18)	0.094
Rituximab	0.27 (0.11 to 0.66)	0.004	0.10 (0.01 to 0.77)	0.027
Other bDMARDs	0.62 (0.38 to 1.01)	0.055	0.57 (0.28 to 1.14)	0.11
Glucocorticoids	0.69 (0.46 to 1.04)	0.076	0.96 (0.56 to 1.65)	0.89
Cessation/reduction of antirheumatic medications at the time of vaccination	4.76 (3.44 to 6.58)	<0.001	2.24 (1.33 to 3.78)	0.002

For 'Outcome: flare', the total N was 7336 (272 flares); for 'Outcome: new medication or dosage increase due to flare', some outcome data were missing, and the total N was 5287 (121 flares). Missing values for vaccine type and disease activity were derived by multiple imputation using full conditional specification.
bDMARDs, biological disease-modifying antirheumatic drugs; I-RMD, inflammatory rheumatic and musculoskeletal disease; TNFi, tumour necrosis factor inhibitors; tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs.

medications such as methotrexate and rituximab was associated with a decreased probability of flare (both for flares in general as well as for flares requiring starting a new antirheumatic medication or change the dose of a current medication). Flares were also more likely to occur in younger patients and females, and less likely to occur with non-Pfizer/AstraZeneca/Moderna vaccines; however, these associations were only observed for flares in general, but not for flares requiring starting a new antirheumatic medication or change the dose of a current medication.

The reported incidences of flare and need to start a new antirheumatic medication or to increase the dosage of an existing medication are in line with the initial results of the EULAR COVAX Registry, where we reported incidences of 4.4% and 1.5%, respectively.[8] Other studies have reported similar or higher incidences, up to 26.7%, depending on the definition of flare (including patient or physician reported), study methodology and study population investigated.[11–23] The highest incidence of flare (26.7%) was reported in a small group of 191 individuals with autoimmune rheumatic diseases who reported minimal clinically important worsening in the 10-item PROMIS physical function form.[17] Importantly, the reported incidences of flare and need to start a new antirheumatic medication or to increase the dosage of an existing medication are not beyond the expected underlying risk of flare based on the natural history of I-RMDs.[27 28]

Post-vaccination flares in individuals with I-RMDs may occur with any vaccination, possibly due to non-specific adjuvant effects or molecular mimicry triggering immune activation, leading to dysregulation of both adaptive and innate immune responses. This dysregulation may involve disordered nucleic acid metabolism and abnormal interferon-induced gene signatures via the TLR-7/9 pathways, contributing to robust early innate immune responses.[29] Our findings confirm that while flares in I-RMDs following SARS-CoV-2 vaccination are possible, they are infrequently observed.

In our study, younger age and female sex were found to be more likely associated with flare occurrence. Several studies have explored the association between demographic factors and post-SARS-CoV-2-vaccination flare. For example, in a patient-reported study assessing risk factors for flare requiring treatment after COVID-19 vaccination, female sex emerged as a significant predictor, while age did not show a significant association with flare.[20] Other studies have reported the association of age and sex with SARS-CoV-2 vaccination-related flare as non-significant factors.[12 15 17] These discrepancies should be interpreted taking into account differences in mean age, sex distribution, disease types, and other study-related methods and characteristics.

o specific disease group was identified as associated with flare. Likewise, another study[15] found that specific I-RMD subgroups were not a risk factor for flare. However, a patient-reported study suggested that certain diseases, such as SLE, PsA and PMR, were associated with higher odds of flare, while idiopathic inflammatory myopathies were associated with lower odds of

flare compared with RA.[20] Data regarding which rheumatic diseases or disease groups are more prone to flare are limited.

The relationship between vaccine type and flare has been depicted differently across various studies. In our study, we showed that vaccination with other vaccines (excluding Pfizer, AstraZeneca and Moderna) was less likely to be associated with flare. This observation should be interpreted with caution, given the low number of non-Pfizer/AstraZeneca/Moderna vaccines administered and the potential reporting bias. Some studies reported higher flare incidence with AstraZeneca[20] and Moderna,[17] while others did not report a relationship between vaccine type and flare.[15 30]

Importantly, we found that higher disease activity and cessation/reduction of antirheumatic medications before or after vaccination were associated with an increased probability of flare, both for flares in general as well as for flares requiring starting a new antirheumatic medication or change the dose of a current medication. This finding highlights the importance of I-RMD control when considering vaccination schedules. There is limited knowledge on post-vaccination disease flare in patients with active disease. The potential mechanism underlying post-vaccination flare in such patients may result from persistent immune pathway dysregulation, even during periods of low disease activity, further exacerbated by vaccination. While EULAR recommendations suggest that vaccination should preferably be administered during quiescent disease states,[31] in the context of a severe pandemic like COVID-19, vaccination is crucial irrespective of disease activity state.

The knowledge regarding the use, reduction or discontinuation of antirheumatic drugs in the context of SARS-CoV-2 vaccination is still scarce. Both EULAR and the American College of Rheumatology (ACR) provided recommendations on these drugs. Unlike the ACR, which recommends withholding certain drugs, including methotrexate, JAK inhibitors, abatacept, mycophenolate mofetil and rituximab, in patients with controlled disease,[24] EULAR does not recommend temporarily reducing or holding any of these drugs except for rituximab.[6 32] A recent randomised trial investigated the effects of a 2-week discontinuation of methotrexate in patients with RA following administration of an inactivated SARS-CoV-2 vaccine. The study found that discontinuing methotrexate improved the anti-SARS-CoV-2 IgG response; however, methotrexate discontinuation was also associated with an increase in disease flares after vaccination compared with patients who continued methotrexate.[33] Similarly, in an open-label, multicentre, randomised-controlled superiority trial involving individuals with immune-mediated inflammatory diseases, including RA, psoriasis with or without arthritis, axSpA, atopic dermatitis, PMR and SLE, a 2-week interruption of methotrexate therapy resulted in increased antibody responses against the receptor-binding domain of the SARS-CoV-2 spike protein, although with a short-term significant increase in the risk of disease flare after COVID-19 booster vaccination compared with continued methotrexate therapy.[34] The clinical significance of interruption of methotrexate after vaccination and improved humoral response is yet to be determined (ie, the clinical impact of this strategy in terms of protection against SARS-CoV-2 infection or prevention of worse COVID-19 outcomes is still unknown), and a shared decision process is needed to weigh the potential benefit of enhancing the humoral response against SARS-CoV-2 against the potential risk of I-RMD exacerbation.

Finally, in our study, patients exposed to methotrexate, TNF inhibitors (overall flare rate only) and rituximab had a lower incidence of flares in our study. In another study,[12] receiving csDMARDs or biological therapy was associated with a lower incidence of flares, while in another study, use of mycophenolate mofetil and glucocorticoids was also linked to lower flare incidences.[17] However, a cross-sectional study of patients with SLE found no significant association between flare and SLE medications.[14] It is known that some immunosuppressive or immunomodulatory drugs reduce seroconversion rates, rendering the vaccine less immunogenic and potentially impacting flare rates.[4]

This study has limitations. First, there is potential selection bias since the COVAX Registry relies on voluntary case reporting; however, this could in principle have led to over-reporting of flares and AEs; therefore, the low rate of flares consistent with other publications is reassuring. Second, as the data are collected from multiple centres across Europe, they represent subjective evaluations across different settings that could influence results, particularly regarding disease activity and flare assessment. Third, time between vaccination and case reporting is also variable, limiting data interpretation and not allowing us to draw any conclusions regarding the long-term safety profile of vaccines against SARS-CoV-2. Fourth, for some signs/symptoms, it can be difficult to determine if the event should be considered an I-RMD flare or simply a transient reactogenicity effect of the vaccine (eg, polyarthralgia); in our study, this decision was left to the reporting physician, which can be considered a study limitation. Importantly, no causal conclusions regarding vaccination and the development of flares can firmly be drawn from this dataset. The strengths of the current study lie in its clinician-reported nature, the large number of patients, provision of multicentre and international real-life data, and detailed examination of clinical and demographic factors associated with flare across various rheumatic diseases.

In conclusion, our findings suggest that disease flare following SARS-CoV-2 vaccination in individuals with immune-mediated rheumatic diseases (I-RMDs) is uncommon. Higher disease activity and cessation/reduction of antirheumatic medications before or after vaccination were associated with an increased probability of flare, while exposure to certain medications such as methotrexate and rituximab was associated with a decreased probability of flare. These findings will assist patients, clinicians and other healthcare professionals in making informed decisions regarding the management of I-RMDs in the context of SARS-CoV-2 vaccination and contribute to the development of the most appropriate vaccination strategies for patients with I-RMDs.

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Ethics approval 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.

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