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## ORIGINAL RESEARCH

## Immune-mediated inflammatory diseases after anti-SARS-CoV-2 vaccines: new diagnoses and disease flares

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### ABSTRACT

**Objective** New-onset immune-mediated inflammatory diseases (IMIDs) and flares of pre-existing IMIDs have been reported following anti-SARS-CoV2 vaccination. Our study aimed at describing a retrospective cohort of patients developing new-onset IMIDs or flares of known IMIDs within 30 days after any anti-SARS-CoV2 vaccine dose.

**Methods** We evaluated clinical records of all inpatients and outpatients referring to our institution between February 2021 and February 2022 with any clinical manifestations. We then selected those having received any anti-SARS-CoV2 vaccine dose within the prior 30 days and classified them as having or not a previous IMID according to predefined criteria. We recorded new-onset IMIDs or flares of known IMIDs and investigated any relationship with demographic, clinical and serological variables.

**Results** 153 patients that received any anti-SARS-CoV2 vaccine dose within the previous 30 days were included of which 45 (29%) already had a diagnosis of IMID while 108 (71%) had no previously diagnosed IMID. 33 (30%) of the 108 patients, were diagnosed with a new-onset IMID. Pericarditis, polymyalgia rheumatica and vasculitis were the most frequent conditions. Among the 45 patients that already had an IMID, disease flare was the reason for referral in 69% of patients. Patients with an IMID flare had a lower number of comorbidities and tended to be younger compared with those who developed other conditions after anti-SARS-CoV2 vaccination.

**Conclusion** We provided a retrospective overview of a cohort of patients who developed new-onset IMIDs or flares of known IMIDs within 30 days after any dose of anti-SARS-CoV2 vaccine. While vaccination campaigns proceed, postvaccination surveillance programmes are ongoing and hopefully will soon clarify whether a causal relationship between vaccines and new-onset/flares of IMIDs exists.

### INTRODUCTION

Over the last decades, evidence on the association between vaccinations and autoimmunity has accrued. Such evidence mainly

### WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Mass vaccination represents the turning point against the pandemic; however, anti-SARS-CoV2 vaccines may induce various adverse reactions like other vaccines and medicinal products.
- ⇒ New-onset autoimmune manifestations and flares of pre-existing immune-mediated inflammatory diseases (IMIDs) following anti-SARS-CoV2 vaccination are being reported but solid evidence of a causal relationship is still lacking.

### WHAT THIS STUDY ADDS

- ⇒ This is one of the largest unselected cohorts of patients developing new-onset IMID or flares of pre-existing IMID following anti-SARS-CoV2 vaccination.
- ⇒ Pericarditis, polymyalgia rheumatica and vasculitis are the most frequently observed new-onset IMID.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Clinicians should be aware that fully blown IMIDs as well as autoimmune features not fulfilling the available classification criteria may occur shortly after anti-SARS-CoV2 vaccination in previously healthy people.
- ⇒ While postvaccination surveillance programmes and ongoing follow-up will ensure data collection on these associations to assess causality, anti-SARS-CoV2 vaccination campaigns should proceed due to the strong efficacy evidence in reducing the virus spread and protecting against severe forms of COVID-19.

pertained to human papillomavirus, hepatitis B and influenza vaccines which were suggested as triggers of aberrant autoimmune responses.<sup>1-3</sup> However, since 2019, the worldwide spreading of SARS-CoV2 infection led to the prompt development of new vaccines and as the vaccination campaign spreads out, a consistent amount of data on

the safety of these vaccines has been collected. As of 21 June 2022, 24 vaccines are currently in use<sup>4</sup> and 11 912 594 538 vaccine doses have been administered worldwide.<sup>5</sup> Among the available compounds developed using different platforms, mRNA-based (BNT162b2, mRNA-1273) and adenovirus vector (ChAdOx1, Ad26.COV2.S) vaccines are those most broadly used and adverse reactions to SARS-CoV2 vaccination have been reported in association with both types of vaccines. Besides mild self-limiting adverse events such as injection site pain, some other adverse events raised concerns in the scientific community and in the public. In March 2021, the European Medicines Agency described a worrisomely high number of cases of thrombocytopenia associated with cerebral venous sinus thrombosis after the administration of the ChAdOx1 vaccine. A pathogenic mechanism similar to heparin-induced thrombocytopenia was postulated and the subsequent demonstration of circulating anti-factor 4 (PF4)–heparin antibodies confirmed the autoimmune nature of this vaccine-induced condition.<sup>6</sup> Vaccine-induced immune thrombotic thrombocytopenia (VITT) was subsequently described also in association with mRNA-based vaccines alongside other vaccine-induced immune-mediated inflammatory diseases (IMIDs) such as autoimmune liver diseases and IgA nephropathy among others.<sup>7–9</sup> However, whether the association between anti-SARS-CoV2 vaccine and new-onset IMIDs is causal or coincidental is still a matter of debate.<sup>10</sup>

Here, we provide a retrospective overview of inpatients and outpatients referring to our institution who developed new-onset IMIDs or flares of known IMIDs.

## METHODS

### Patient cohort

Clinical records of all inpatients and outpatients referring to either our Internal Medicine and Nephrology ward or our Immuno-Rheumatology service at the University of L'Aquila, Italy, between February 2021 and February 2022 were reviewed. Inclusion and exclusion criteria were in accordance with WHO guidelines for surveillance of adverse events following immunisation<sup>11</sup> which represent a rationale question-based process to identify the eligible cases (online supplemental figure S1). In particular, the entry criterion for the study was having received any anti-SARS-CoV2 vaccine dose within the prior 30 days. Then we classified the included patients as IMID or no-IMID according to the following criteria: no IMID patients had neither a prevaccination diagnosis of IMID nor a prevaccination clinical suspicion of IMID leading to specific laboratory and clinical assessment. Among IMID patients, those with a flare who discontinued or reduced for more than 30 days the immunosuppressive therapy prior vaccination were excluded.

### Statistical analysis

Data were analysed with IBM-SPSS V.28 software. Variables were compared using either the  $\chi^2$  test or the

Mann-Whitney U test as needed. Bivariate correlation (Spearman's  $\rho$ ) and binary logistic regression analysis were also performed. All tests were two tailed and values of  $p < 0.05$  were considered statistically significant.

## RESULTS

Between February 2021 and February 2022, 2519 patients were admitted to our institution (either the Internal Medicine and Nephrology ward or our Immuno-Rheumatology service) with various clinical manifestations. Among these, we identified 153 patients (105 inpatients and 48 outpatients) that received any anti-SARS-CoV2 vaccine dose within the 30 days before admission. Two out of 105 inpatients deceased during in-hospital stay.

Of these 153 patients, 45 (29%) already had a diagnosis of IMID while 108 (71%) had no previously diagnosed IMID (table 1). Of these 108 patients, 88 were inpatients and 20 were outpatients. A new-onset IMID was diagnosed in 33 (30%) of the 108 patients. However, when assessing the data according to the setting, new-onset IMID were diagnosed in 13/88 (15%) inpatients and 20/20 (100%) outpatients (table 1). None of these 33 patients had familiar history of IMID. When comparing the patients developing or not a new-onset IMID, we did not observe any difference with regard to gender, type of anti-SARS-CoV2 vaccine, number of doses received prior to the symptom onset, age, duration of in-hospital stays or number/type of comorbidities.

Table 2 shows the prevalence of the presenting complaints of the 88 inpatients without previous IMID. Abdominal pain (with or without diarrhoea), fatigue, fever and dyspnoea were the most frequent reasons for admission of inpatients regardless of the diagnosis at discharge. Conversely chest pain was more frequently reported by inpatients subsequently diagnosed with IMID ( $p < 0.001$ ). As shown in table 3, 20 outpatients with no history of IMID that subsequently were diagnosed with IMID, were referred mainly for arthralgia, arthritis, myalgia, pain and stiffness of the shoulder and hip girdle, erythematous cutaneous lesions and morning stiffness.

Table 4 shows the newly diagnosed IMIDs in the 33 patients and the number of doses received prior IMID diagnosis. With regard to the timing of symptom onset, online supplemental table S1 shows that symptoms in the majority of patients with new-onset IMIDs occurred within the first week after vaccination regardless of the number of doses received. Furthermore, all the patients developing a new-onset IMID after three vaccine doses reported symptoms as early as week 1.

With regard to autoantibodies, both patients with autoimmune thrombocytopenia displayed antiplatelet antibodies but not anti-PF4 antibodies, while of the two patients with antiphospholipid syndrome (APS) one displayed high titers of both anticardiolipin and anti-beta2GPI IgG antibodies but a negative lupus anticoagulant (LAC) and the other displayed a positive LAC but neither anticardiolipin nor anti-beta2GPI IgG antibodies.

**Table 1** Characteristics of the study cohort of patients without immune-mediated inflammatory disease (IMID) and according to the subsequent diagnosis of IMID or other condition

	All (N=108)	New-onset IMID (N=33)	No new-onset IMID (N=75)	P value*
Inpatients	88 (81)	13 (39)	75 (100)	<0.0001
Outpatients	20 (19)	20 (61)	0 (0)	
M	65 (60)	20 (61)	45 (60)	0.95
F	43 (40)	13 (39)	30 (40)	
Vaccine type†				0.07
BNT162b2	71 (66)	18 (54)	53 (71)	
mRNA-1273	11 (10)	4 (12)	7 (9)	
ChAdOx1	18 (17)	10 (30)	8 (11)	
Ad26.COV2.S	7 (6)	1 (4)	6 (8)	
Unknown	1 (1)	0 (0)	1 (1)	
Doses received prior to IMID diagnosis				
1	NA	9	NA	NA
2		16		
Full-schedule+booster‡		8		
Age, mean±SD	64±17	62±16	65±17	0.42
In-hospital stay, days, mean±SD	14±9	12±9	15±9	
Comorbidities, median (range)	3 (0–7)	2 (0–7)	3 (0–6)	0.14
Type of comorbidity, N (%) of patients				
Cardiovascular diseases		17 (52)	49 (65)	0.18
Respiratory diseases		2 (6)	13 (17)	0.12
Metabolic disorders		11 (33)	16 (21)	0.18
Gastrointestinal diseases		5 (15)	18 (24)	0.3
Renal diseases		2 (6)	9 (12)	0.34
Neurological diseases		4 (12)	12 (16)	0.6
Endocrine diseases		12 (36)	24 (32)	0.66
Urogenital diseases		2 (6)	7 (9)	0.57
Non-inflammatory MSK diseases		3 (9)	11 (15)	0.43
Neoplasms		4 (12)	8 (11)	0.82
Dermatological diseases		1 (3)	0 (0)	0.54
Psychiatric diseases		0 (0)	3 (4)	0.8
Ophthalmological diseases		0 (0)	3 (4)	0.8
Haematological disorders		1 (3)	2 (3)	0.91
ENT diseases		0 (0)	3 (4)	0.8

Values are shown as number (%) of patients unless otherwise stated.

BNT162b2, vaccine developed by Pfizer/BioNTech; mRNA1273, vaccine developed by Moderna; ChAdOx1 nCoV-19, vaccine developed by AstraZeneca; Ad26.COV2.S, vaccine developed by Janssen; NA, not applicable; SD, standard deviation; MSK, musculoskeletal; ENT, ear nose throat.

\*New-onset IMID versus No new-onset IMID. P values were calculated with  $\chi^2$  test or Mann-Whitney U test as needed.

†This refers to the dose(s) received prior to the booster vaccination.

‡Booster dose was BNT162b2 in 2/8 patients and mRNA-1273 in 6/8 patients.

ENT, ears, nose and throat; MSK, musculoskeletal; N, number; NA, not applicable; SD, standard deviation.

Both patients with RA were seropositive, one displayed a positive rheumatoid factor (RF) without anticyclic citrullinated peptide (anti-CCP) while the other had positive anti-CCP and negative RF. The patient with microscopic polyangiitis displayed high titers of antiproteinase 3

antibodies. The patient with autoimmune thyroiditis displayed anti-thyroid antibodies. No autoantibody positivity was detected in the other patients with new-onset IMID.

**Table 2** Reasons for referral of inpatients without previous immune-mediated inflammatory disease (IMID) according to the discharge diagnosis of IMID or other diseases

	New-onset IMID (N=13)		No now onset IMID (N=75)	
	N	%	N	%
Fever	3	23	15	20
Dyspnoea	4	31	11	15
Cough	0	0	3	4
Fatigue	0	0	15	20
Nausea/vomiting	0	0	9	12
Syncope/pre-syncope	0	0	7	9
Chest pain*	4	31	1	1
Abdominal pain/diarrhoea	3	23	22	29
Anorexia/weight loss	0	0	4	5
Melaena	0	0	2	3
Arthralgia	1	8	2	3
Back pain	0	0	4	5
Arthritis	1	8	2	3
Lower limbs deep vein thrombosis	1	8	2	3
Pulmonary fibrosis	1	8	0	0
Purpura	1	8	0	0
Muscle weakness	1	8	0	0
Thrombocytopenia	1	8	1	1
Dizziness	0	0	2	3
Jaundice	0	0	2	3
Numbness	0	0	2	3
Confused state	0	0	4	5
Ankle oedema	0	0	3	4
Erythematous cutaneous lesions	0	0	2	3
Fall without loss of consciousness	0	0	2	3
Acute kidney insufficiency	0	0	2	3
Other symptoms/signs†	0	0	7	9

\*P=0.00086.

†Displayed by only one patient out of the 75 with no new-onset IMID and by no patient out of the 13 subsequently diagnosed with IMID. These symptoms/signs included: macroscopic haematuria, ab-ingestis pneumonitis, burning mouth syndrome, respiratory failure, headache, oliguria, oesophageal varices.

On initiation of the appropriate treatment for the newly-diagnosed IMID, all patients improved. However, one of the two subjects diagnosed with APS developed APS-related retinal artery thrombosis and ultimately loss of vision.

**Table 3** Reasons for referral of outpatients without previous immune-mediated inflammatory disease (IMID) that were subsequently diagnosed with IMID

Manifestation	N	%
Arthralgia	8	40
Increase of acute phase reactants	8	40
Arthritis	5	25
Myalgia	4	20
Pain and stiffness of the shoulder and hip girdle	3	15
Erythematous cutaneous lesions	3	15
Morning stiffness	3	15
Fatigue	2	10
Back pain	2	10
Visual disturbances	2	10
New-onset thrombocytopenia	2	10
Numbness	1	5
Dizziness	1	5
Malaise	1	5
Chest pain	1	5
Headache	1	5

Table 5 shows the features of the 45 patients with pre-existing IMID (N=17 inpatients; N=28 outpatients) and the reasons for referral, among which an IMID flare was the most frequent (31/45, 69%). Patients with a disease flare had a lower number of comorbidities (p=0.04), although no differences in the type of comorbidities was observed, and tended to be younger than those who developed other vaccine-related conditions (table 6). All the 3 patients who were referred after the booster dose showed a disease flare. In addition, we observed numerical differences, although not significant, with regard to the clinical picture that occurred after the first or second dose of the regular vaccination schedule. In fact, in about half of the patients who experienced a disease flare it happened after the first dose and in about 30% after the second dose. Conversely, other vaccine related conditions appeared mainly after the second dose (71% of patients), to a lesser extent after the first dose (29%) and never after the third dose. With regard to the timing of flare onset, online supplemental table S2 shows that they occurred within the first week after vaccination regardless of the number of doses received.

Finally, regarding flare outcomes, 21 (68%) patients had a complete response to the treatment, 2 (6%) had a partial response and 8 (26%) had no response requiring further adjustment of treatment.

## DISCUSSION

As of 21 June 2022, 136 206 350 doses of anti-SARS-CoV2 vaccines have been administered in Italy. This corresponds to a coverage of 85.2% of the population with

**Table 4** Type of new-onset immune-mediated inflammatory disease (IMID), N=33

New-onset IMID	N (%) of patients	Vaccine doses before IMID onset N (%) of patients		
		1	2	3
Pericarditis	5 (14)	0	4 (80)	1 (20)
Polymyalgia rheumatica	4 (11)	0	0	4 (100)
Vasculitis*	4 (11)	1 (25)	2 (50)	1 (25)
Undifferentiated arthritis	3 (8)	1 (33)	1 (33)	1 (33)
Autoimmune thrombocytopaenia	3 (8)	1 (33)	1 (33)	1 (33)
Anti-phospholipid syndrome	2 (5)	1 (50)	1 (50)	0
Psoriatic arthritis	2 (5)	1 (50)	1 (50)	0
Spondyloarthritis	2 (5)	1 (50)	1 (50)	0
Rheumatoid arthritis	2 (5)	2 (100)	0	0
Ulcerative colitis	1 (3)	0	1 (100)	0
Adult-onset autoimmune enteropathy	1 (3)	0	1 (100)	0
Crystal arthritis	1 (3)	0	1 (100)	0
Cholangitis	1 (3)	0	1 (100)	0
Autoimmune thyroiditis	1 (3)	0	1 (100)	0
Optic neuritis	1 (3)	1 (100)	0	0

\*n=1 Giant cell arteritis, n=1 IgA vasculitis (Schönlein-Henoch), n=1 leucocytoclastic vasculitis, n=1 microscopic polyangiitis.

**Table 5** Characteristics of patients with pre-existing immune-mediated inflammatory disease and reason for referral

Pre-existing IMID (N=45)				
Condition	N (%)	Reasons for referral	Inpatients, N	Outpatients, N
Sjögren's syndrome	15 (33)	IMID flare	7	24
PsA	10 (22)	Fever	0	2
Psoriasis	6 (13)	Nausea/vomiting	1	1
Autoimmune thyroiditis	5 (11)	Diarrhoea	2	1
Rheumatoid arthritis	4 (9)	Abdominal pain	1	1
UCTD	2 (4)	Melena	1	0
IBD	2 (4)	Fatigue	2	0
Type 1 diabetes	2 (4)	Visual disturbances	0	1
AI hepatitis	2 (4)	Jaundice	1	0
Vasculitis	1 (2)	Dyspnoea	1	0
Behçet disease	1 (2)	Electrolyte imbalance	1	0
Crystal arthritis	1 (2)	Septic arthritis	1	0
PMR	1 (2)	Retinal thrombosis	1	0
Sarcoidosis	1 (2)	Tuberculous spondylodiscitis	1	0
SLE	1 (2)	Anaemia	1	0
SpA	1 (2)			
Multiple sclerosis	1 (2)			
MCTD	1 (2)			

AI, Autoimmune; IBD, inflammatory bowel disease; MCTD, mixed connective tissue disease; N, number; PMR, polymyalgia rheumatica; PsA, psoriatic arthritis; SLE, systemic lupus erythematosus; SpA, spondyloarthritis; UCTD, undifferentiated connective tissue disease.



**Table 6** Characteristics of patients with pre-existing immune-mediated inflammatory disease (IMID) according to the reason for referral (disease flare or other)

	All (N=45)	Disease flare (N=31)	Other (N=14)	P value*
Inpatients, N (%)	17	7	10	0.002
Outpatients, N (%)	28	24	4	
Male, N (%)	9	5	4	0.33
Female, N (%)	36	26	10	
Vaccine type, N (%)†				0.45
BNT162b2	37	26	11	
mRNA-1273	5	5	0	
ChAdOx1	2	0	2	
Ad26.COV2.S	1	0	1	
Doses received prior to IMID diagnosis				0.25
1	21	17	4	
2	21	11	10	
Full-schedule+booster†	3	3	0	
Age, mean±SD	62±13	61±13	67±9	0.12
Comorbidities, median (range)	4 (1–7)	4 (1–7)	5 (3–7)	0.04
Type of comorbidity, N (%) of patients				
Cardiovascular diseases	24 (53)	15 (48)	9 (64)	0.65
Respiratory diseases	8 (18)	5 (16)	3 (21)	0.67
Metabolic disorders	9 (20)	8 (26)	1 (7)	0.15
Gastrointestinal diseases	11 (24)	6 (19)	5 (36)	0.24
Renal diseases	3 (7)	2 (6)	1 (7)	0.93
Neurological diseases	5 (11)	3 (10)	2 (14)	0.65
Endocrine diseases	21 (47)	15 (48)	6 (43)	0.73
Urogenital diseases	3 (7)	1 (3)	2 (14)	0.17
Non-inflammatory MSK diseases	13 (29)	9 (29)	4 (29)	0.97
Neoplasms	1 (2)	1 (3)	0 (0)	0.55
Dermatological diseases	4 (9)	2 (6)	2 (14)	0.39
Psychiatric diseases	6 (13)	4 (13)	2 (14)	0.89
Ophthalmological diseases	1 (2)	1 (3)	0 (0)	0.55
Haematological disorders	2 (4)	2 (6)	0 (0)	0.93
ENT diseases	1 (2)	1 (3)	0 (0)	0.55
>1 IMID	6 (13)	5 (16)	1 (7)	0.41

\*Patients who developed a disease flare versus patients with other vaccine-related diagnoses. P values were calculated with  $\chi^2$  test or Mann-Whitney U test as needed. BNT162b2, vaccine developed by Pfizer/BioNTech; mRNA1273, vaccine developed by Moderna; ChAdOx1 nCoV-19, vaccine developed by AstraZeneca; Ad26.COV2.S, vaccine developed by Janssen.

†Booster dose was BNT162b2 in 3/3 patients.

ENT, ears, nose and throat; MSK, musculoskeletal.

a least one dose (including single-dose vaccines) and 80.4% of the population with two doses.<sup>5</sup> Although it is evident that vaccines have considerably reduced the incidence of serious manifestations linked to the SARS-CoV2 infection and that the mass vaccination represents the turning point against the pandemic, a broad spectrum of vaccine-induced manifestations, including new-onset IMIDs, have been reported. We described a retrospective cohort of 153 patients that were admitted to our

institution within 30 days of the vaccine dose. Of these, 33 patients were diagnosed with new-onset IMID. In more detail, new-onset IMIDs were diagnosed in all the 20 patients referring for the first time to our Immunology-Rheumatology service with clinical suspicion of IMID. Conversely, although only 4 of the 88 inpatients admitted to our internal medicine ward within 30 days from any anti-SARS-CoV2 vaccine dose had a clinical suspicion of

IMID, we ultimately diagnosed an IMID in 13 of the 88 patients.

The main mechanisms through which anti-SARS-CoV2 vaccine may trigger autoimmunity include molecular mimicry, the production of autoantibodies and the role of vaccine adjuvants.<sup>10</sup> As demonstrated for other vaccines such as human papilloma virus and influenza, the cross-reaction between viral proteins and tissue auto-antigens may lead to the development of an aberrant autoimmune response by means of molecular mimicry. However, the low incidence of vaccine-induced IMIDs underscores the importance of genetic predisposition to facilitate the disease development only in a small subgroup of vaccinated people. This process may also occur with regard to anti-SARS-CoV2 vaccine due to the similarity of SARS-CoV2 proteins and tissue antigens. With regard to the production of autoantibodies, VITT represents an example of antibody-mediated vaccine-induced IMID that deserves to be discussed. Initially believed to pertain only to adenovirus vector vaccines, VITT was subsequently described also in association with mRNA-based vaccines.<sup>7</sup> Patients with VITT display antibodies targeting PF-4 and mediating their effect through IgG-FcγR interactions and complement activation.<sup>12,13</sup> Of interest, however, vaccine induced anti-PF4 do not cross-react with the SARS-CoV2 spike protein.<sup>14</sup> Finally, vaccine adjuvants as well as the mRNA included in vaccines may trigger autoimmunity via the inflammasome pathway being recognised by toll like receptors.<sup>15</sup> On this basis, anti-SARS-CoV2 vaccine-induced IMIDs represent a challenge for clinicians since the interaction between the vaccine and the immune system needs to be fully elucidated while patients may develop not only fully blown IMIDs but also autoimmune features not fulfilling the available classification criteria.

In our cohort, the most frequent new-onset IMID was pericarditis (14%), followed by polymyalgia rheumatica (PMR) (11%) and vasculitis (11%).

As far as pericarditis is concerned, we previously reported a series of patients who developed pericarditis after a median of 20 days from clinical and virological recovery from SARS-CoV-2 infection.<sup>16</sup> Conversely in the current patient cohort, pericarditis developed between 10 and 15 days after the second (N 4/5) or third (N=1/5) dose of an mRNA vaccine.

Our data on PMR are somehow in line with the results of a multicentre Italian study reporting PMR-like features as the most common clinical picture observed in rheumatology settings within 4 weeks after an anti-SARS-CoV2 vaccine dose.<sup>17</sup> In the study from Ursini *et al* PMR-like features occurred after the first or the second dose of either mRNA-based or adenovirus-based vaccines. In addition, a case report from Manzo *et al* also described new-onset PMR after the administration of the first dose of an mRNA-based vaccine.<sup>18</sup> Conversely, in our cohort all cases of PMR occurred after the third vaccine dose and all patients had received mRNA-based vaccines.

To date, several cases of vasculitis occurring after any anti-SARS-CoV2 vaccine have been reported ranging

from giant cell arteritis, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, cutaneous lymphocytic vasculitis and IgA vasculitis.<sup>19–24</sup> In our retrospective cohort, we observed 4 cases of new-onset vasculitis. Three patients received the ChAdOx1 vaccine while one received the Ad26.COV2.S vaccine. Of interest, all the cases that followed the ChAdOx1 vaccine (one GCA, one leukocytoclastic vasculitis and one ANCA-associate vasculitis) occurred after the first dose while the case that followed the Ad26.COV2.S vaccine (IgA vasculitis) occurred after the booster dose with an mRNA-based vaccine.

The link between ChAdOx1 vaccine and new-onset vasculitis may recognise a role for both molecular mimicry/adjuvant effects and endothelial damage. In fact, during acute SARS-CoV-2 infection vasculitis may be induced by direct endothelial damage. As mentioned above, ChAdOx1 vaccine can induce anti-PF4 antibodies and therefore interfere with the endothelial/coagulation homeostasis.<sup>19</sup> With regard to autoantibodies, it is important to mention that none of the three patients developing thrombocytopenia in our cohort (two of which after ChAdOx1 vaccine) displayed anti-PF4 antibodies but rather they tested positive for antiplatelet antibodies hence being diagnosed with autoimmune thrombocytopenia.

Arthralgia is rather common after any anti-SARS-CoV2 vaccines, occurring in up to 30% of people.<sup>25,26</sup> Arthritis is less frequent; however, it is not necessarily a red flag for a subsequent diagnosis of IMID. In fact, reports of new-onset chronic inflammatory arthritis are scarce and mainly pertain to rheumatoid arthritis (RA).<sup>27</sup> It is important to mention, however, that since RA autoantibodies may occur years before the clinical phase of the disease, it is not possible to rule out whether anti-SARS-CoV2 vaccine induced only the articular manifestations or also a seroconversion.

Finally with regard to patients with a pre-existing IMID that developed post-vaccine symptoms, the most frequent cause for referral was a disease flare (69%). A recent systematic literature review of studies enrolling vaccinated patients with RMDs found no postvaccination disease flare in 868 patients.<sup>28</sup> Conversely, a report from the European Alliance of Associations for Rheumatology COVAX registry (N=1375) and the COVID-19 Global Rheumatology Alliance Vaccine Survey Group (N=5619) described a disease flare in about 5% of patients, of whom only a minority experienced a severe flare or requiring a change in treatment.<sup>29,30</sup> Differences concerning disease type and activity, ongoing treatment, discontinuation/reduction of immunosuppressive therapy prior vaccination, comorbidities, demographic factors and vaccine type may account for the variability of these data.

The main limitation of our study is its retrospective nature, therefore our results need to be integrated with evidence from future controlled, prospective studies.

In conclusion, anti-SARS-CoV2 vaccines may induce various adverse reactions like other vaccines and medicinal products. In particular, evidence of new-onset IMIDs

and IMIDs flares has accrued but post vaccination surveillance programmes, population-based and prospective clinical studies are needed to ensure data collection on these associations to assess causality. Solid evidence on the mechanisms of interaction between vaccine and immune system, the role of genetic predisposition, disease type and activity, ongoing treatment and other variables, will shed additional light on the controversial link between anti-SARS-CoV2 vaccine and autoimmunity. Nonetheless, with billions of individuals worldwide now immunised with a least one dose of an anti-SARS-CoV2 vaccine, real-life observational data are in line with evidence from clinical trials and support their efficacy and safety.

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