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ORIGINAL RESEARCH

# Inflammatory rheumatic diseases with onset after SARS-CoV-2 infection or COVID-19 vaccination: a report of 267 cases from the COVID-19 and ASD group

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## ABSTRACT

**Objectives** To better define the spectrum of new-onset post-COVID-19 and post-COVID-19 vaccine inflammatory rheumatic diseases (IRD) from a large multicentric observational study.

**Methods** Consecutive cases of IRD encountered during a 12-month period and satisfying one of the following inclusion criteria: (a) onset of the rheumatic manifestations within 4 weeks from SARS-CoV-2 infection or (b) onset of the rheumatic manifestations within 4 weeks from the administration of one of the COVID-19 vaccines ws recruited.

**Results** The final analysis cohort comprised 267 patients, of which 122 (45.2%) in the post-COVID-19 and 145 (54.8%) in the postvaccine cohort. Distribution of IRD categories differed between the two cohorts: the post-COVID-19 cohort had a higher percentage of patients classified as having inflammatory joint diseases (IJD, 52.5% vs 37.2%, p=0.013) while the post-vaccine cohort had a higher prevalence of patients classified as polymyalgia rheumatica (PMR, 33.1% vs 21.3%, p=0.032). No differences were detected in the percentage of patients diagnosed with connective tissue diseases (CTD 19.7% vs 20.7%, p=0.837) or vasculitis (6.6% vs 9.0%, p=0.467). Despite the short follow-up period, IJD and PMR patients' response to first-line therapy was favourable, with both groups achieving a drop in baseline disease activity scores of ~30% and ~70% respectively.

**Conclusion** Our article reports the largest cohort published to date of new-onset IRD following SARS-CoV-2 infection or COVID-19 vaccines. Although causality cannot be ascertained, the spectrum of possible clinical manifestations is broad and includes IJD, PMR, CTD and vasculitis.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Since the beginning of the COVID-19 pandemic, isolated cases of inflammatory rheumatic diseases (IRD) with onset after SARS-CoV-2 infection or COVID-19 vaccine administration have been described by several groups. However, the anecdotical nature of the previous reports does not allow to catch the 'big picture' of the spectrum of IRD potentially associated with those exposures.

### WHAT THIS STUDY ADDS

⇒ In this study, we collected a large cohort of IRD developed in close temporal association with SARS-CoV-2 infection or vaccine administration. According to our data, the spectrum of possible presentation is broad and includes inflammatory joint diseases (IJD), polymyalgia rheumatica (PMR), connective tissue diseases (CTD) and vasculitis with IJD prevailing in post-COVID-19 and PMR prevailing in postvaccine patients.

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

⇒ Our study provides a broad, descriptive analysis of the possible array of IRD associated with SARS-CoV-2 infection and COVID-19 vaccines. This may contribute to strengthen the awareness on similar events—although uncommon—among physicians involved in musculoskeletal care and stimulate further research on this topic.

## INTRODUCTION

Following the rapid spread of the COVID-19 pandemic, the scientific community demonstrated an unprecedented resilience to tackle an unknown biological threat, obtaining rapid progress in understanding the pathogenesis of the disease[1] and the subsequent development of highly specific 'countermeasures' such as the novel mRNA vaccines[2] and antiviral medications.[3] This allowed to scale down the burden of the disease and save tens of millions of lives globally.[4] Indeed, most European countries achieved large vaccine coverage and Italy, in particular, attained one of the most successful campaigns with more than 50 million of people (93% of the population >12 years) getting at least one dose.[5]

Since the beginning, it was evident that the profound interaction between SARS-CoV-2 and the host immune system[1] drives the most severe acute manifestations of the disease (eg, acute respiratory distress syndrome and microvascular injury); on the other hand, in the subsequent phases, a long-term immune dysregulation was demonstrated in at least a proportion of patients[6] that may bolster prolonged symptoms persisting for months or years after viral clearance.

Postacute COVID-19 syndrome (PACS)[7] has now been defined as an extremely heterogeneous condition following COVID-19 and characterised by a multitude of signs and symptoms including complaints of rheumatological interest.[8] Musculoskeletal pain, indeed, is reported in almost 10% of individuals infected by SARS-CoV-2 at some time during the first year after the infection[8] and, as suggested in a previous study published by our group, most of these patients satisfy the classification criteria for fibromyalgia.[9]

Concurrently, a growing number of articles described new-onset serological evidence of autoimmunity[10 11] or frank inflammatory rheumatic diseases (IRD)—including inflammatory joint diseases (IJD),[12] polymyalgia rheumatica (PMR),[13] connective tissue diseases (CTD)[14 15] and vasculitis[16]—in close temporal association with SARS-CoV-2 infection. However, this was not surprising as the potential role of infections in triggering rheumatic diseases has been hypothesised since decades on the basis of preclinical studies[17] and is clearly recapitulated by reactive arthritis[18] or virally induced arthritis (eg, parvovirus B19 or hepatitis C virus (HCV)).[19] On the other hand, it was previously speculated that also the exposure to vaccines may elicit autoimmunity.[20] The controversial autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome),[21] in example, is believed to result from the exposure to common vaccine adjuvants. Also in this case, reports of IRD following vaccination with available anti-COVID-19 vaccines appeared in literature since the earliest phases of the vaccine campaign.[22–25]

On this background, aim of the present study was to contribute to the knowledge on the spectrum of new-onset post-COVID-19 and post-COVID-19 vaccine IRD with a descriptive and comparative analysis from a large multicentric observational study.

## METHODS

### Study design and inclusion/exclusion criteria

The present study was conceived as an observational cohort study. To this purpose, we published a web-based data collection form and invited all members of the Italian *COVID-19 and autoimmune systemic diseases* (COVID-19 and ASD) collaborative research group[26] to submit consecutive cases of IRD or acrosyndrome encountered during routine clinical practice from 1 November 2021 to 31 October 2022 (12 months) and satisfying one of the following inclusion criteria: (a) onset of the rheumatic manifestations within 4 weeks from SARS-CoV-2 infection, demonstrated by RT-PCR and/or antigenic nasopharyngeal swab or (b) onset of the rheumatic manifestations within 4 weeks from the administration of one of the COVID-19 vaccines approved for administration in Italy (BNT162b2—Pfizer/BioNTech), mRNA-1273 (Moderna) during the collection period. Exclusion criteria were predefined as a past history of IRD or acrosyndrome or a diagnosis of PACS or 'long-COVID'.

The COVID-19 and ASD group is a network of more than 40 physicians with senior experience in the management of patients with IRD, belonging to 11 public academic medical centres, 7 public general hospitals, 3 private academic medical centres and 2 private general hospitals, covering regions from northern to southern Italy and including rheumatologists, clinical immunologists and specialists in internal medicine.

Data were collected anonymously through an online form built using the Google Forms platform. Google Forms is a free and easy to use questionnaire administration tool that has been largely used in medical research.[27] Cases submitted by individuals centres were assigned an alphanumeric identifier code, including a centre-specific string and a progressive patient number; before the analysis, records were manually checked for recognising potential duplicate entries (eg, identical demographic data and/or other variables despite different identifier code).

Information gathered included demographic characteristics, past exposure to SARS-CoV-2 infection, vaccine status, clinical features of rheumatological interest, autoantibodies status, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), final diagnosis of the rheumatologist, first-line treatment.

For patients classified as having arthritis, disease activity before and after at least 4 weeks of treatment was recorded using the disease activity score including 28 joints (DAS28).[28] For patients classified as having PMR, disease activity before and after at least 4 weeks of treatment was recorded using the PMR activity score (PMR-AS) as previously published.[29]

The research was conducted in compliance with the Declaration of Helsinki and its latest amendments[30] and approved by a central Ethics Committee (Comitato Etico Azienda Sanitaria Locale 1 Avezzano/Sulmona/L'Aquila, L'Aquila, Italy; approval number: 0204194/22). Written informed consent was obtained from all study subjects.

### Statistical analysis

Data are expressed as mean±SD, median (25th–75th percentile) or number (percentage) as appropriate. Student's t test was used to compare differences in normally distributed continuous variables between the two groups; highly skewed variables were *ln*-transformed before the analysis. Fisher's exact test was used to compare categorical variables. A p value <0.05 was considered statistically significant. All analyses were performed using the SPSS software V.26.0 (IBM, Armonk, New York).

## RESULTS

### Clinical features of the overall study population

A total of 270 cases were entered in the database. Three records were excluded because identified as mechanical pain related to osteoarthritis (n=1) or fibromyalgia (n=2). No duplicate records were identified. The final analysis cohort comprised a total of 267 patients, of which 122 (45.2%) patients in the post-COVID-19 (age 54±17 years, 69.7% female subjects) and 145 (54.8%) patients (age 58±16 years, 66.2% female subjects) in the postvaccine cohort. Number of vaccine doses received did not differ between post-COVID-19 and postvaccine patients (2±1 vs 3±1, p=0.123).

In the post-COVID-19 cohort, four (3.3%) patients experienced asymptomatic infection, 104 (85.2%) had mildly symptomatic disease, while 14 (11.5%) had severe disease according to the WHO severity classification.[31] Accordingly, 113 patients (92.6%) were treated at home and only 9 (7.4%) were hospitalised; of these, only one required subsequent admission to intensive care unit.

In the postvaccine cohort, most cases occurred after the booster (third) dose (n=66, 45.8%); the remaining were associated with a second dose (n=51, 35.4%), first dose (n=23, 16%) and only three (2.1%) after a fourth dose. In most cases, the specific vaccine associated with IRD onset was the Pfizer/BioNTech BNT162b2 (n=114, 78.6%) followed by Moderna mRNA-1273 (n=24, 16.6%), mirroring the overall distribution of COVID-19 vaccines dispensed in Italy.[5] In seven (4.8%) patients, the specific vaccine was unknown. A total of 15 (10.3%) patients reported a history of asymptomatic or mildly symptomatic COVID-19 before the vaccine dose associated with IRD onset.

Mean delay between COVID-19 diagnosis or vaccine administration and rheumatic manifestations development was 14.5±7.8 vs 13.9±8.5 days, respectively (p=0.59).

Distribution of various IRD categories differed between the two cohorts (figure 1): the post-COVID-19 cohort had a higher percentage of patients classified as having IJD (52.5% vs 37.2%, p=0.013), while the postvaccine cohort had a higher prevalence of patients classified as PMR (33.1% vs 21.3%, p=0.032). No differences were detected in the percentage of patients diagnosed with CTD (post-COVID-19: 19.7% vs postvaccine: 20.7%, p=0.837) or vasculitis (post-COVID-19: 6.6% vs postvaccine: 9.0%, p=0.467).

### Inflammatory joint diseases

The most represented IRD category in both groups was IJD. The range of specific IJD was broad (table 1), with peripheral spondyloarthritis (pSpA), representing the most frequent final diagnosis. Although IJDs were relatively more frequent in post-COVID-19 patients, a significantly higher proportion of patients in the postvaccine group was diagnosed as having PsA (29.6% vs 12.5%, p=0.021), while no significant differences were observed in other domains, including baseline inflammatory markers, disease activity, follow-up duration and first-line treatment used. The two patients in the post-COVID-19 vaccine cohort classified as having adult-onset Still's disease (AOSD) were included as part of the IJD subgroup because of a predominantly articular clinical picture. Notably, despite the short follow-up, patients' response to first-line therapy was favourable, with both

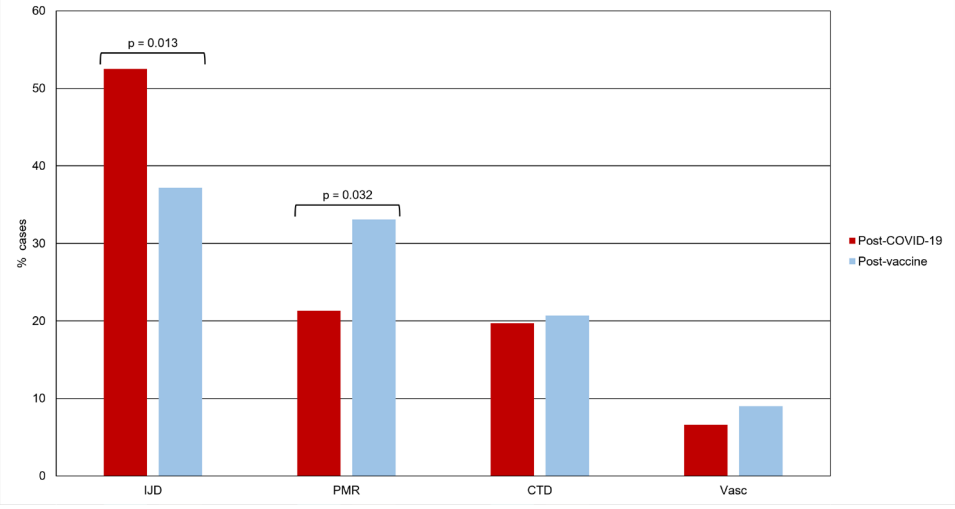


**Figure 1** **Relative frequencies of inflammatory rheumatic diseases categories in the two study cohorts.** CTD, connective tissue diseases; IJD, inflammatory joint diseases; PMR, polymyalgia rheumatica; Vasc, vasculitis.

**Table 1** Comparative analysis of clinical features in inflammatory joint diseases with onset after SARS-CoV-2 infection or COVID-19 vaccine administration

| | Post-COVID-19 (n=64) | Post-vaccine (n=54) | P value |
|---|---|---|---|
| Age, years | 49±14 | 51±13 | 0.277 |
| Female sex, n (%) | 47 (73.4) | 37 (68.5) | 0.557 |
| N° vaccine doses, n | 2±1 | 3±1 | 0.434 |
| ESR (baseline), mm/h | 32±22 | 36±25 | 0.364 |
| ESR (follow-up), mm/h | 19±12 | 20±14 | 0.689 |
| CRP (baseline), mg/dL | 1.29 (1.00–2.50) | 1.50 (0.56–2.50) | 0.639 |
| CRP (follow-up), mg/dL | 0.53 (0.40–0.90) | 0.50 (0.30–0.80) | 0.456 |
| TJC (baseline), n | 6±4 | 8±6 | 0.081 |
| TJC (follow-up), n | 3±3 | 3±4 | 0.895 |
| SJC (baseline), n | 2 (2–4) | 3 (2–4) | 0.754 |
| SJC (follow-up), n | 0 | 0 | 0.575 |
| DAS28-CRP (baseline), score | 4.3±1.0 | 4.4±1.1 | 0.501 |
| DAS28-CRP (follow-up), score | 3.0±1.0 | 3.1±1.1 | 0.887 |
| Average follow-up, weeks | 8 (6–12) | 8 (7–12) | 0.866 |
| Specific diseases | | | |
| pSpA (other than PsA), n (%) | 32 (50.0) | 19 (35.2) | 0.106 |
| HLA-B27 present, n (%) | 8 (25) | 6 (31.6) | 0.748 |
| Enthesitis, n (%) | 4 (12.5) | 1 (5.3) | 0.401 |
| Dactylitis, n (%) | 3 (9.4) | 1 (5.3) | 0.597 |
| RA, n (%) | 19 (29.7) | 14 (25.9) | 0.650 |
| RF positive, n (%) | 11 (57.9) | 10 (71.4) | 0.486 |
| ACPA positive, n (%) | 10 (52.6) | 7 (50.0) | 1.000 |
| PsA, n (%) | 8 (12.5) | 16 (29.6) | 0.021 |
| Enthesitis, n (%) | 3 (37.5) | 8 (50.0) | 0.562 |
| Dactylitis, n (%) | 1 (12.5) | 4 (25.0) | 0.477 |
| AxSpA, n (%) | 5 (7.8) | 3 (5.6) | 0.627 |
| HLA-B27 present, n (%) | 3 (60.0) | 2 (66.7) | 1.000 |
| Enthesitis, n (%) | 1 (20.0) | 0 (0.0) | 0.408 |
| Dactylitis, n (%) | 0 (0.0) | 0 (0.0) | 1.000 |
| AOSD, n (%) | 0 (0.0) | 2 (3.7) | 0.120 |
| Treatment | | | |
| Paracetamol, n (%) | 8 (12.5) | 13 (24.1) | 0.101 |
| NSAIDs, n (%) | 30 (46.9) | 22 (40.7) | 0.504 |
| GCs, n (%) | 33 (51.6) | 33 (61.1) | 0.298 |
| Intra-articular GCs, n (%) | 1 (1.6) | 3 (5.6) | 0.232 |
| Colchicine, n (%) | 2 (3.1) | 0 (0.0) | 0.190 |
| MTX, n (%) | 22 (34.4) | 22 (40.7) | 0.476 |
| SSZ, n (%) | 9 (14.1) | 3 (5.6) | 0.128 |
| HCQ, n (%) | 4 (6.3) | 5 (9.3) | 0.540 |
| TNFi, n (%) | 3 (4.7) | 0 (0.0) | 0.107 |
| ANR, n (%) | 0 (0.0) | 1 (1.9) | 0.274 |

ANR, anakinra; AOSD, adult-onset Still's disease; AxSpA, axial spondyloarthritis; CRP, C reactive protein; DAS28, disease activity score including 28 joints; ESR, erythrocyte sedimentation rate; GCs, glucocorticoids; HCQ, hydroxychloroquine; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; PsA, psoriatic arthritis; pSpA, peripheral spondyloarthritis; RA, rheumatoid arthritis; SJC, swollen joint count; TJC, tender joint count; TNFi, TNF inhibitors.

**Table 2** Comparative analysis of clinical features in polymyalgia rheumatica with onset after SARS-CoV-2 infection or COVID-19 vaccine administration

| | Post-COVID-19 (n=28) | Post-vaccine (n=46) | P value |
|---|---|---|---|
| Age, years | 58±20 | 62±17 | 0.632 |
| Female sex, n (%) | 5 (62.5) | 9 (69.2) | 0.751 |
| N° vaccine doses, n | 2±1 | 2±1 | 0.739 |
| ESR (baseline), mm/h | 50±22 | 59±32 | 0.150 |
| ESR (follow-up), mm/h | 22±18 | 22±15 | 0.954 |
| CRP (baseline), mg/dL | 2.15 (1.46–4.10) | 1.99 (1.62–3.09) | 0.630 |
| CRP (follow-up), mg/dL | 0.60 (0.50–1.00) | 0.50 (0.50–0.95) | 0.910 |
| PMR-AS (baseline), score | 28.3 (25.2–33.0) | 24.8 (23.7–27.5) | 0.392 |
| PMR-AS (follow-up), score | 8.44 (5.4–10.0) | 6.43 (4.6–7.0) | 0.268 |
| Average follow-up, weeks | 8±5 | 14±13 | 0.004 |
| Treatment | | | |
| Paracetamol, n (%) | 1 (3.6) | 4 (8.7) | 0.666 |
| NSAIDs, n (%) | 2 (7.1) | 7 (15.2) | 0.303 |
| GCs, n (%) | 28 (100.0) | 43 (93.5) | 0.168 |
| MTX, n (%) | 2 (7.1) | 9 (19.6) | 0.145 |

CRP, C reactive protein; ESR, erythrocyte sedimentation rate; GCs, glucocorticoids; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; PMR-AS, polymyalgia rheumatica—activity score.

groups achieving a 30% drop from baseline in disease activity, as measured by DAS28-CRP.

### Polymyalgia rheumatica

PMR was the second most common IRD category (table 2). None of the patients had clinical features reminiscent of concurrent giant cell arteritis (GCA) or required second-level imaging for suspected GCA on the basis of clinical judgement; those patients with prominent symptoms and/or supporting imaging suggestive of GCA with or without associated PMR are reported in the vasculitis subgroup.

No significant differences were observed between post-COVID-19 and postvaccine PMR patients, except for a shorter duration of follow-up in the post-COVID-19 patients (8±5 vs 14±13 weeks, p=0.004). Despite this, the patients responded well to first-line therapy, with reductions in PMR-AS of 70% and 74% from baseline, respectively. Of note, six patients in the postvaccine and one in the post-COVID-19 cohort were aged below 50 years (range: 33–48). However, all patients had increased CRP (range: 1.15–5.4 mg/dL) and/or ESR levels (range: 20–110 mm/hour), a clear PMR-like clinical presentation, and steroid responsiveness (overall PMR-AS: baseline 23.5±2.3 vs follow-up 7.7±2.8) and thus were attributed to the PMR subgroup by the treating rheumatologist.

### Connective tissue diseases

CTDs were also frequently reported. The range of specific CTD presentation was broad (table 3) and included undifferentiated CTD, systemic sclerosis, idiopathic inflammatory myopathies, amyopathic dermatomyositis, systemic lupus erythematosus, mixed CTD, Sjogren's syndrome and isolated new-onset acrosyndrome. Notably, when comparing the two cohorts, the only variable reaching statistical significance was the prevalence of acrosyndrome, which was greater in post-COVID-19 group (20.8 vs 3.3%, p=0.02). No information on the follow-up of CTD patients was collected due to the high heterogeneity between outcome measures in such a mixed category of patients.

### Vasculitis

Vasculitis was the least common category in both groups. However, the range of specific presentation was broad (table 4) and included small-vessel vasculitis, large-vessel vasculitis, variable vessel vasculitis and isolated skin vasculitis. No significant differences were found when comparing post-COVID-19 and postvaccine patients. No information on the follow-up of vasculitis patients was collected due to the high heterogeneity between outcome measures in such a mixed category of patients.

## DISCUSSION

Since the earliest phases of the pandemic, several isolated case reports or small case series reporting the suspicious onset of rheumatic diseases in association with SARS-CoV-2 infection or COVID-19 vaccine administration have been published. Even though the anecdotal nature of those reports did not shed sufficient light on this phenomenon, they represent a stimulating hypothesis-generating basis for encouraging additional research on this topic.

**Table 3** Comparative analysis of clinical features in connective tissue diseases with onset after SARS-CoV-2 infection or COVID-19 vaccine administration

| | Post-COVID-19 (n=24) | Post-vaccine (n=30) | P value |
|---|---|---|---|
| Age, years | 47±18 | 55±19 | 0.134 |
| Female sex, n (%) | 19 (79.2) | 22 (73.3) | 0.618 |
| N° vaccine doses, n (%) | 2±1 | 3±1 | 0.263 |
| ANA positive, n (%) | 21 (87.5) | 28 (93.3) | 0.462 |
| >1:160, n (%) | 12 (57.1) | 16 (57.1) | 1.000 |
| >1:640, n (%) | 3 (14.3) | 5 (17.8) | 1.000 |
| ESR, mm/h | 19±16 | 28±22 | 0.728 |
| CRP, mg/dL | 0.75 (0.30–1.50) | 0.56 (0.20–2.50) | 0.551 |
| Specific diseases | | | |
| UCTD, n (%) | 6 (25.0) | 11 (36.7) | 0.359 |
| Anti-SSA positive, n (%) | 0 (0.0) | 3 (27.3) | 0.159 |
| Anti-Scl-70 positive, n (%) | 2 (33.3) | 2 (18.2) | 0.482 |
| SSc, n (%) | 6 (25.0) | 6 (20.0) | 0.661 |
| Anti-Scl-70 positive, n (%) | 2 (33.3) | 2 (33.3) | 1.000 |
| ACA positive, n (%) | 3 (50.0) | 4 (66.7) | 0.558 |
| IIM, n (%) | 4 (16.7) | 6 (20.0) | 0.754 |
| Anti-Mi2 positive, n (%) | 1 (25.0) | 2 (33.3) | 0.778 |
| Anti-PI7 positive, n (%) | 1 (25.0) | 0 (0.0) | 0.197 |
| Anti-TIF1-γ, n (%) | 0 (0.0) | 2 (33.3) | 0.197 |
| ADM, n (%) | 0 (0.0) | 2 (6.7) | 0.197 |
| Anti-Mi2 positive, n (%) | 0 (0.0) | 1 (50.0) | N/A* |
| Anti-MDA5 positive, n (%) | 0 (0.0) | 1 (50.0) | N/A* |
| SLE, n (%) | 2 (8.3) | 1 (3.3) | 0.425 |
| Anti-ds-DNA positive, n (%) | 1 (50.0) | 1 (100.0) | 0.386 |
| Anti-Sm positive, n (%) | 1 (50.0) | 0 (0.0) | 0.386 |
| MCTD, n (%) | 0 (0.0) | 3 (10.0) | 0.111 |
| Anti-RNP positive, n (%) | 0 (0.0) | 3 (100.0) | N/A* |
| SjS, n (%) | 1 (4.2) | 0 (0.0) | 0.259 |
| SSA positive, n (%) | 1 (100.0) | 0 (0.0) | N/A* |
| Isolated acrosyndrome, n (%) | 5 (20.8) | 1 (3.3) | 0.042 |
| Acrocyanosis, n (%) | 2 (40.0) | 0 (0.0) | 0.439 |
| Raynaud's phenomenon, n (%) | 3 (60.0) | 1 (100.0) | 0.439 |
| Treatment | | | |
| Paracetamol, n (%) | 7 (29.2) | 10 (33.3) | 0.743 |
| NSAIDs, n (%) | 5 (20.8) | 6 (20.0) | 0.940 |
| GCs, n (%) | 9 (37.5) | 17 (56.7) | 0.161 |
| Intra-articular GCs, n (%) | 2 (8.3) | 0 (0.0) | 0.107 |
| Colchicine, n (%) | 0 (0.0) | 3 (10.0) | 0.111 |
| MTX, n (%) | 3 (12.5) | 3 (10.0) | 0.771 |
| HCQ, n (%) | 4 (16.7) | 6 (20.0) | 0.754 |
| AZA, n (%) | 0 (0.0) | 2 (6.7) | 0.197 |
| MMF, n (%) | 1 (4.2) | 1 (3.3) | 0.872 |
| CYC, n (%) | 0 (0.0) | 1 (3.3) | 0.367 |
| IVIg, n (%) | 1 (4.2) | 1 (3.3) | 0.472 |
| CCBs, n (%) | 4 (16.7) | 2 (6.7) | 0.245 |

*Expected number in one category is equal to zero.
ACA, anti-centromere antibodies; ADM, amyopathic dermatomyositis; ANA, antinuclear antibodies; AZA, azathioprine; CCBs, calcium channel blockers; CRP, C reactive protein; CYC, cyclophosphamide; ESR, erythrocyte sedimentation rate; GCs, glucocorticoids; HCQ, hydroxychloroquine; IIM, idiopathic inflammatory myopathy; IVIg, intravenous immunoglobulin; MCTD, mixed connective tissue disease; MMF, mycophenolate mofetil; MTX, methotrexate; N/A, not applicable; NSAIDs, non-steroidal anti-inflammatory drugs; SjS, Sjögren's syndrome; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; UCTD, undifferentiated connective tissue disease.

To contribute to the body of knowledge in this field, we systematically collected consecutive cases of IRD onset in close temporal association with COVID-19 or vaccine administration, in order to identify potential differences between the two cohorts and more accurately depict the spectrum of diseases.

According to our results, IRD may occur roughly equivalently both following SARS-CoV-2 infection or COVID-19 vaccination and the range of manifestations is broad, covering different forms of IJD, CTD or vasculitis. However, it is crucial to disclose that temporal association alone does not imply causality and may merely represent a coincidental association, and, thus, no pathophysiological explanation can be extrapolated from ours' and others' available data. Furthermore, although we report a similar number of cases in the two cohorts, it must be pointed out that the denominator of the overall population is not known, preventing any epidemiological consideration to be drawn. Anyway, from a merely speculative point of view and according to the Italian Ministry of Health official data, 25 millions of cases of COVID-19 have been registered to date while more than 143 million of doses of COVID-19 vaccines have been administered.[5] This implies that the number of individuals potentially susceptible to vaccine-related events is at least fivefold higher than that exposed to SARS-CoV-2 infection. Consequently, the association is anticipated to occur more frequently by coincidence in the postvaccination cohort (ie, no more than the anticipated number of incident cases of the specific IRD in such a heavily immunised population).

**Table 4** Comparative analysis of clinical features in vasculitis with onset after SARS-CoV-2 infection or COVID-19 vaccine administration

| | Post-COVID-19 (n=8) | Post-vaccine (n=13) | P value |
|---|---|---|---|
| Age, years | 58±20 | 62±17 | 0.632 |
| Female sex, n (%) | 5 (62.5) | 9 (69.2) | 0.751 |
| N° vaccine doses, n | 2±1 | 2±1 | 0.739 |
| ANA positive, n (%) | 2 (25) | 4 (30.8) | 0.776 |
| ESR, mm/h | 42±33 | 67±46 | 0.162 |
| CRP, mg/dL | 3.57±2.80 | 5.48±5.89 | 0.329 |
| Specific diseases | | | |
| Large vessel vasculitis, n (%) | 2 (25.0) | 3 (23.1) | 0.920 |
| C-GCA, n (%) | 1 (12.5) | 2 (15.4) | 0.854 |
| LV-GCA, n (%) | 1 (12.5) | 1 (7.7) | 0.716 |
| Small vessel vasculitis, n (%) | 3 (37.5) | 3 (23.1) | 0.477 |
| ANCA positive, n (%) | 2 (66.7) | 1 (33.3) | 0.414 |
| EGPA, n (%) | 2 (66.7) | 2 (66.7) | 1.000 |
| GPA, n (%) | 0 (0.0) | 1 (33.3) | 0.273 |
| MPA, n (%) | 1 (33.3) | 0 (0.0) | 0.273 |
| Variable vessel vasculitis, n (%) | 0 (0.0) | 1 (7.7) | 0.421 |
| BD, n (%) | 0 (0.0) | 1 (7.7) | N/A* |
| Skin vasculitis, n (%) | 3 (37.5) | 6 (46.2) | 0.697 |
| Palpable purpura, n (%) | 2 (66.7) | 6 (100.0) | 0.134 |
| Urticarial vasculitis, n (%) | 1 (33.3) | 0 (0.0) | 0.134 |
| Treatment | | | |
| NSAIDs, n (%) | 1 (12.5) | 2 (15.4) | 0.854 |
| GCs, n (%) | 6 (75.0) | 12 (92.3) | 0.271 |
| Colchicine, n (%) | 0 (0.0) | 1 (7.7) | 0.421 |
| MTX, n (%) | 1 (12.5) | 0 (0.0) | 0.191 |
| SSZ, n (%) | 1 (12.5) | 0 (0.0) | 0.191 |
| AZA, n (%) | 2 (25.0) | 1 (7.7) | 0.271 |
| CYC, n (%) | 0 (0.0) | 1 (7.7) | 0.421 |
| ANR, n (%) | 0 (0.0) | 1 (7.7) | 0.421 |

*Expected number in one category is equal to zero.
ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies; ANR, anakinra; AZA, azathioprine; BD, Behçet's disease; C-GCA, cranial giant cell arteritis; CRP, C reactive protein; CYC, cyclophosphamide; EGPA, eosinophilic granulomatosis with polyangiitis; ESR, erythrocyte sedimentation rate; GCs, glucocorticoids; GPA, granulomatosis with polyangiitis; LV-GCA, large vessel giant cell arteritis; MPA, microscopic polyangiitis; MTX, methotrexate; N/A, not applicable; NSAIDs, non-steroidal anti-inflammatory drugs; SSZ, sulfasalazine.

Additionally, increase in disease activity following SARS-CoV-2 infection has been reported in a significant portion of patients with pre-existent IRD,[32 33] but it is difficult to uncouple the direct role of the virus and/or secondary immune system activation from the consequences of background DMARD treatment disruption. Similarly, vaccine administration has been associated with worsening of disease activity in a minor, but still present, fraction of patients.[34 35] In this context, although it is not possible to exclude that a small proportion of patients in our cohort may actually represent a SARS-CoV-2 or vaccine-induced exacerbation of latent or previously undiagnosed IRD, evidence of disease flare-up in previously diagnosed IRD patients may suggest common underling pathophysiological mechanisms, leading to the development of a true, 'de novo', immunopathological event.

Despite these limitations, our data provide an interesting overview of the spectrum of the diseases possibly associated with either SARS-CoV-2 infection or COVID-19 vaccine and highlight some potential differences between the two cohorts. Indeed, we found a relatively higher percentage of patient developing IJD after COVID-19, while, on the other hand, a higher percentage of vaccine recipients developed PMR. Conversely, the distribution of other IRD categories did not differ between the two groups.

Viruses are well-known triggers for acute, subacute or chronic arthritis as commonly occur after parvovirus B19, HCV or chikungunya virus infection.[36] A previous report from our group[25] suggested that the delay between COVID-19 and arthritis onset is associated with the clinical phenotype of arthritis: while an RA-like pattern (polyarthritis mainly involving wrist and hand)—reminiscent of other prototypical viral arthritis—was more common in patients with early onset of rheumatic manifestations after infection (≤2 weeks), a late onset was more frequently associated with oligoarthritis of large joints suggestive of reactive arthritis. Viral infections have been evoked as a potential pathophysiological contributor to a number of other autoimmune diseases with different mechanisms including, but not limited to, molecular mimicry, bystander activation and epitope spreading.[37]

Similarly to infections, vaccine administration has been associated with the development of autoimmunity.[38] The debated ASIA syndrome[21] was defined in 2011 by Shoenfeld and collaborators as a condition in which the exposure to an adjuvant (eg, aluminium-based or squalene) leads to an abnormal, autoimmunogenic, immune response. However, it must be pointed out that novel mRNA vaccines do not contain traditional adjuvants because nucleic acids are sufficiently immunogenic to induce an effective immunisation.[39]

Our findings regarding post-vaccine IRD are in line with available literature, demonstrating that PMR is the most reported IRD after COVID-19 vaccine administration.[25 40 41] Similar data were previously reported for influenza vaccine[42 43] and supposed to result from an external trigger leading to an aberrant response in the context of a senescent immune system. Similarly to what observed in the post-COVID-19 cohort, however, in the post-vaccine group we reported a number of other ARD belonging to all categories mirroring isolated case reports or small

series available in literature.[22 44–46] Furthermore, a growing body of evidence support an association between mRNA vaccines and non-rheumatic autoimmune diseases such as myopericarditis,[47 48] while adenovirus-based vaccines have been associated with vaccine-induced immune thrombotic thrombocytopenia[49 50] and Guillain-Barré syndrome.[51 52]

Interestingly, when comparing clinical features of IJD between the two cohorts, we observed a higher relative percentage of PsA in the post-vaccine cohort. There are no obvious explanations for this finding although both new-onset psoriasis and psoriasis flares have been reported following COVID-19 vaccination.[53] A speculative interpretation may be that the presence of concurrent skin disease (either new-onset or exacerbation of previously unrecognised psoriasis) promoted by vaccine administration, may lead to classify as PsA some patients of the post-vaccine cohort that otherwise would be attributed to the pSpA category. Unfortunately, we did not collect information regarding the cutaneous domain and therefore no sub-analysis can contribute to interpret this finding.

Another interesting finding is the higher prevalence of new-onset acrosyndromes in post-COVID-19 patients. This finding is not unsurprising in the light of the well-described endothelial tropism of SARS-CoV-2[54] ; indeed, cutaneous microvascular changes have been described since the beginning of the pandemic as chilblain-like lesions or 'COVID toes'.[55] In a Spanish observational study, acro-ischaemic lesions were observed in 0.6% outpatients and 2.9% hospitalised COVID-19 patients.[56] More recently, Sulli *et al*[57] reported that the mean nail-fold capillary number per linear millimetre was significantly lower in COVID-19 survivors when compared with primary Raynaud's phenomenon patients and control individuals.

In conclusion, although the aforementioned limitations, our article reports the largest cohort published to date and supports the hypothesis that new-onset IRD may be triggered by SARS-CoV-2 infection or COVID-19 vaccines and that the spectrum of possible clinical manifestations is broad and includes IJD, PMR, CTD and vasculitis. However, it is highly plausible that the risk conferred by SARS-CoV-2 infection is higher and thus the usefulness and safety of vaccines, in our opinion, are not to be questioned. Larger epidemiological studies are needed to better clarify the causal role of each individual exposure on this association, quantify the true incidence and eventually explore the pathophysiological mechanism linking SARS-CoV-2 infection or vaccination to the development of IRD.

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