New onset and flare of rheumatic diseases following COVID-19 vaccination are mild and respond well to treatment: 9-month follow-up data from a single centre cohort

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Abstract

Objective

Anti-COVID-19 vaccines have proved to be effective and well tolerated. Great attention is now being paid to the characterisation of possible adverse events associated to their administration. We report a case series of suspected rheumatic diseases (RDs) following anti-COVID-19 vaccination.

Methods

We included patients evaluated at first-aid rheumatologic consultancy and at rheumatologic outpatient and inpatient clinic at Padova University Hospital between May and September 2021 presenting with a RD within 30 days after an anti-COVID-19 vaccine dose. Our selection was in accordance with the World Health Organisation guidelines for adverse event following immunisation (AEFI) surveillance. Patients were regularly re-evaluated by telemedicine or face-to-face visit.

Results

We identified 30 cases of RD following vaccination: 24 (80.0%) new onsets and 6 (20.0%) flares. Most of patients (76.6%) received the BNT162b2 vaccine. The mean time to RD onset/flare was 12±9 days. The most common manifestations were inflammatory arthritis (40.0%), rheumatic polymyalgia (33.3%) and adult-onset Still's disease (13.3%). At the last FU visit (9.6±2.2 months), 83.3% of patients showed complete response to first- or second-line therapy, 13.3% a partial response and one patient (3.3%) was still experiencing an active disease.

Conclusion

Considering the amount of vaccine doses administered during the evaluation period we overall detected a limited number of cases. We noted a clear prevalence of autoinflammatory conditions and seronegative manifestations. The great majority of patients had mild features and showed a good response to therapy.

Key words

COVID-19 vaccines, adverse effects, rheumatic diseases, inflammation

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Introduction

Since the start of current devastating pandemic researchers have been investigating the short- and long-term consequences related to the severe acute respiratory syndrome – coronavirus 2 (SARS-CoV2) infection. Extensive knowledge has therefore been acquired in SARS-CoV2 biology and virulence but, with the wide implementation of the vaccination campaign, the attention has been chiefly focused on complications potentially related to immunisation, universally defined as 'adverse events following immunisation' (AEFI).

Both viral infections and vaccines are known to be associated with the development of rheumatic diseases (RDs) as they elicit innate and adaptive immune response. Severe SARS-CoV2 infection induce a massive cytokine storm which may elicit the development of reactive manifestations through a molecular mimicry process (1, 2). Likewise, anti-COVID-19 vaccines, although having so far proved an excellent tolerability and safety profile, boost the immune response via different biologic technologies and adjuvant combinations. Based on this, great interest is now arising from rheumatologists to define the impact of infection and SARS-CoV2 immunisation among rheumatic patients (3-5). Here, a descriptive analysis of a monocentric cohort evaluated at Padova University Hospital for a new onset/flare of RD after receiving any anti-COVID-19 vaccine is reported.

Material and methods

We considered all patients evaluated between 1st May and 30th September 2021 at emergency rheumatologic consultancy, rheumatologic outpatient, and inpatient clinic. We selected those presenting with a new-onset RD or a RD flare within 30 days after the first or second dose of an anti-COVID-19 vaccine. Diagnosis was based on clinical assessment; however, classification criteria for RDs were assessed in order to include patients in the study. Serological profile and response to therapy were also considered. We excluded patients with unspecific manifestations such as arthralgias, myalgias or fatigue. Inclusion and exclusion criteria were also in accordance with WHO guidelines for surveillance of AEFI which represents a rationale question-based process to identify eligible cases (6).

We did not consider disease exacerbations in those who discontinued or reduced the immunosuppressive therapy for more than 30 days in view of receiving the vaccine. We instead contemplated patients with a RD in good clinical control or remission before immunisation, based on the physician's assessment.

All patients were reassessed by telemedicine visit or face-to face follow-up (FU) visit between 8 and 12 months from the first medical contact.

Results

Baseline characteristics of our cohort

Based on our inclusion and exclusion criteria we identified 31 patients with a possible AEFI. One patient, who developed cutaneous purpura 8 days after the first dose of ChAdOx1 vaccine, was excluded because he did not fulfil the WHO criteria since further exams showed a hepatitis B infection (Fig. 1). We defined a final cohort of 30 patients: 24 presenting with a new-onset RD and 6 with an exacerbation of their underlying RD (Table I).

The mean age was 64±17 years and the most frequently received vaccine was the BNT162b2 (76.6%). We observed a slightly greater incidence of rheumatic AEFI in females (53.3%). In general, they occurred mostly after the second dose (56.7%) and after a mean of 12±9 days from vaccine administration.

New onset RDs

We mostly observed cases of rheumatic polymyalgia (RPm) (10 cases; 41.6%) (7) and of acute arthritis (9 cases; 37.5%). We also observed 3 cases (12.5%) of adult-onset Still's disease (AOSD) (8), a case of cutaneous purpura and a case of mono-ocular myositis which is indeed a rare condition among RDs. One of the cases of RPm occurred in a patient with dermatomyositis off- immunosuppressive therapy due to clinical remission. One patient diagnosed with AOSD presented with

a macrophage activation syndrome (MAS), responding well to high doses dexamethasone and intravenous IL-1 receptor antagonist (IL-1RA), anakinra. Among the cases of arthritis 2 had a microcrystalline aetiology based on clinical manifestation, ultrasonographic features and ex-juvantibus response to colchicine. The other 7 cases were classified as undifferentiated seronegative arthritis since they did not fulfil any specific classification criteria.

RD flares

We observed a RD exacerbation in 6 cases: one case of AOSD flare, one case of proximal interphalangeal joints hand arthritis in a patient with rheumatoid arthritis (RA), one case of wrist arthritis in a patient with psoriatic arthritis, one of aortitis in a patient with previous giant cell arteritis, one case of polyarthritis in undifferentiated connective tissue disease (UCTD) and one case of inflammatory polyarthralgia and nephritis in systemic lupus erythematosus (SLE). Except for the patients with aortitis and lupus nephritis which required hospitalisation, the others were mild according to the corresponding disease activity scores.

Treatment and FU

First-line treatment was based on systemic glucocorticoids (GC) alone (63.3%), systemic GC plus IL-1RA (13.3%), non-steroidal autoinflammatory drugs (13.3%), intra-articular GC (6.6%) and colchicine (3.3%).

The mean FU time was 9.6±2.2 months, one patient was lost in FU.

During FU evaluation we observed a prompt symptom resolution and/or a decrease of laboratory inflammatory markers in 22 patients (73.3%) after receiving the first-line therapy. Three patients (10%) required adjunctive treatment, in particular colchicine for wrist microcrystalline arthritis, CS joint injection for undifferentiated wrist arthritis and methotrexate for a patient with RPm only partially responsive to CS therapy.

Four patients had an initial improvement but then experienced disease exacerbation after GC withdrawal/discontinuation: one patient with AOSD developed a MAS under anti-IL-1RA therapy and was then switched to anti-IL1ß canakinumab, another patient with AOSD was hospitalised after three months from diagnosis due to developing pachymeningitis responsive to an increased dose of GC, the last two experienced a relapse of RPm symptoms after GC therapy withdrawal and required a resumption of steroid treatment (Table I).

The patient with lupus still had active nephritis at the last FU visit despite mycophenolate mofetil therapy and the introduction of belimumab.

Twenty-five patients (83.3%) completed the primary vaccination cycle with the third vaccine dose without complaining of any further rheumatic symptom.

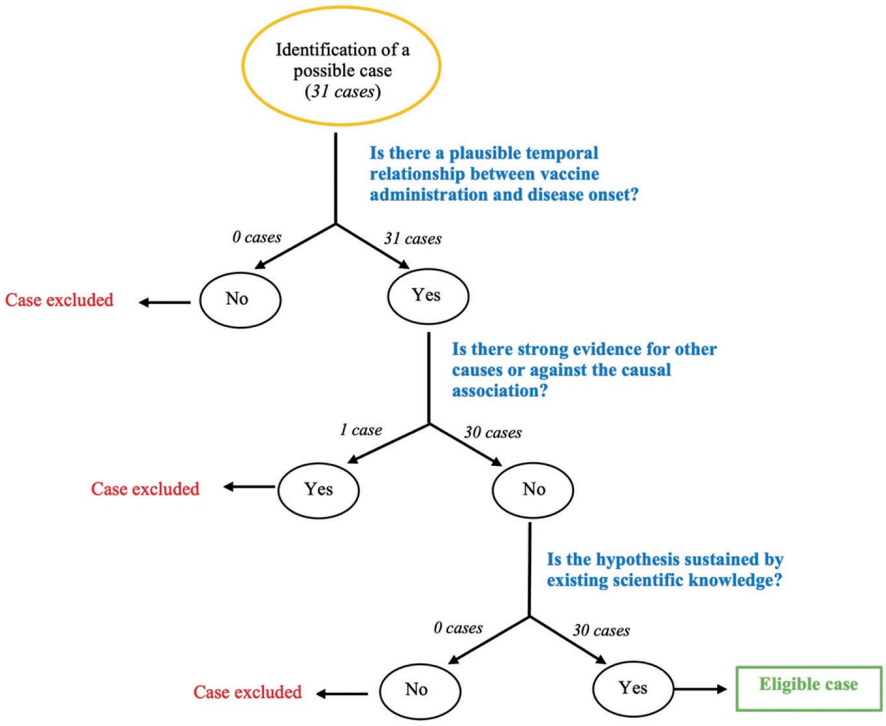

Fig. 1. WHO algorithm for identification of patients with of adverse events following immunisation.

Discussion

By the end of September 2021, the immunisation rate of people over 12 years in a North-East Italian Region (Veneto) reached 77.8% of the population for a total of 6.882.395 administered doses (9). Comparing the total number of AEFI we registered during the observation period to the amount of vaccine doses administered in the reference population (which we consider to be half of the Veneto population) we can speculate that the incidence of rheumatologic AEFI was conceivably low, although we are aware it is an underestimation. Most of the new onset RDs we observed were mild, and with a benign course in 93.3% of cases. Other reports of immune-mediated and inflammatory disease associated with anti-SARS-CoV2 vaccination have recently been published and, in accordance with our observations, describe an excellent response of inflammatory features to first-line standard therapy (10, 11).

Interestingly, most of the RDs observed in our cohort encompass conditions that could be ascribed among the spectrum of inflammatory disorders, predominantly sustained by an innate immune-based pathogenesis. No autoantibody production, marker of active adaptive immune response, was found in any patient with arthritis. The only three cases that are considered autoimmune are among patients with a pre-existing autoimmune condition (SLE, RA and UCTD). The patient with ocular myositis presented a low non-specific ANA titre up to 1:160 but no myositis-specific or associated auto-antibodies.

Potentially an autoinflammatory rather than an autoimmune condition may be

Table I. Analytical description of patient's clinical and epidemiological features.

New onset RD	Age (years)	sex	Pre-existing autoimmune disease	Dose and Type of vaccine received	Rheumatic AEFI developed	Time to AEFI (days)	Months of FU	Lab exams at diagnosis	Lab exams at last FU visit	First line Therapy	Complic-ations after therapy de-escalation	Second line therapy	Clinical response at last FU evaluation	Therapy withdrawal at last FU	Completion of primary vaccination course (3 doses)
1	82	M	No	2nd dose, BNT162b2	RPm	5	11	CRP 120 mg/L	CRP 8.63 mg/L	Oral GC	No	-	Complete	Yes	Yes
2	50	F	Autoimmune hypothyro-dism	1st dose, BNT162b2	AOSD	3	11	Ferritin 6000 ug/L, CRP 280	Ferritin 326 ug/L, CRP 3.3 mg/L	Oral GC + anti-IL1	Hospital-isation for MAS	Canakin-umab	Complete*	No	No
3	65	M	No	1st dose, ChAdOx1	AOSD	10	10	Ferritin 1552 ug/L, CRP 480 mg/L	Ferritin 195 ug/L, CRP < 2.9 mg/L	Oral GC + anti-IL1	Hospital-isation for pachy-meningitis	-	Partial (asthenia)	Yes	No
4	73	F	No	2nd dose, BNT162b	Micro-crystalline wrist arthritis	10	10	CRP 40 mg/L	NA	Intra-articular GC injection	No	Colchicine	Complete*	Yes	Yes
5	75	F	No	1st dose, ChAdOx1	RPm	30	8	CRP 131 mg/L; neg RF and ACPA	CRP < 2.9 mg/L, ESR 28 mm/h	Oral GC	No	-	Complete	Yes	Yes
6	82	M	No	2nd dose, BNT162b2	RPm	5	12	CRP 109 mg/L	NA	Oral GC	No	-	Complete	Yes	Yes
7	61	M	No	1st dose, BNT162b2	Cutaneous purpura	2	12	CRP <2.9 mg/L; neg: ANA, ANCA and RF	CRP < 2.9	Oral GC	No	-	Complete	Yes	Yes
8	52	M	No	1st dose, BNT162b2	Ocular myositis	7	11	CPK 201 U/L, ANA 1:160; neg: RF, anti-ENA and MSA	CPK 97 U/L	Oral GC	No	-	Complete	No	Yes
9	46	M	No	1st dose, BNT162b2	Micro-crystalline 1st PIP hand arthritis	3	9	NA	NA	Colchicine	No	-	Complete	Yes	Yes
10	89	F	No	2nd dose, BNT162b2	RPm	5	11	CRP 130 mg/dL, ESR 118 mm/h, neg RF	CRP 17 mg/L, ESR 48	Oral GC	Symptoms relapse after volunteer GC withdrawal	-	Partial (inflammatory arthralgias)	No	Yes
11	81	F	No	2nd dose, BNT162b2	RPm	20	11	CRP 11 mg/L	CRP 2.9 mg/L	Oral GC	No	-	Complete	No	No
12	70	M	No	2nd dose, ChAdOx1	Undiffer-entiated seronegative polyarthritis	30	11	CRP 21 mg/L, neg RF	CRP 4.5 mg/L	Oral GC	No	-	Complete	Yes	Yes
13	77	M	No	1st dose, ChAdOx1	RPm	15	8	CRP 10 mg/dL, ESR 63 mm/h	CRP 3 mg/L, ESR 11 mm/h	Oral GC	No	-	Complete	No	Yes
14	54	F	No	1st dose, BNT162b2	AOSD (MAS)	1	8	CRP 96 mg/L, Ferritin 223400 ug/L	CRP < 2.9 mg/L Ferritin 50 ug/L	Iv and Oral GC + anti-IL1	No	-	Complete	No	Yes
15	59	M	No	2nd dose, ChAdOx1	RPm	5	10	CRP 18 mg/L	CRP < 2.9 mg/L	Oral GC	No	-	Complete	No	Yes
16	77	M	No	2nd dose, ChAdOx1	Undiffer-entiated seronegative oligoarthritis	30	11	CRP 22 mg/L, neg RF	CRP 12 mg/L,	Oral NSAID	No	-	Complete	Yes	Yes

New onset RD	Age (years)	sex	Pre-existing autoimmune disease	Dose and Type of vaccine received	Rheumatic AEFI developed	Time to AEFI (days)	Months of FU	Lab exams at diagnosis	Lab exams at last FU visit	First line therapy	Complic-ations after therapy de-escalation	Second line therapy	Clinical response at last FU evaluation	Therapy withdrawal at last FU	Completion of primary vaccination course (3 doses)
17	73	F	No	2nd dose, ChAdOx1	Undiffer-entiated seronegative monoarthritis (wrist)	21	8	CRP 16.4-mg/L, ESR 27 mm/h, neg RF	CRP 2.9 mg/L, ESR 32 mm/h	Oral GC	No	Joint CS injection	Complete*	Yes	No
18	55	M	Psoriasis	2nd dose, BNT162b2	Undiffer-entiated seronegative polyarthritis	5	8	CRP 25 mg/L, neg RF	CRP 3 mg/L,	Oral NSAID	No	-	Complete	Yes	Yes
19	66	F	No	2nd dose, BNT162b2	RPm	7	9	CRP 29.6 mg/L, ESR 18 mm/h	CRP 6.9 mg/L, ESR5 mm/h	Oral GC	No	MTX	Complete*	Withdra-wal of oral GC, continuing MTX	Yes
20	73	F	Vitiligous	2nd dose, BNT162b2	Undiffer-entiated seronegative monoarthritis (ankle)	10	8	CRP 21 mg/L; neg RF and ACPA	CRP 5 mg/L,	Oral NSAID	No	-	Complete	Yes	Yes
21	65	M	No	1st dose, BNT162b2	Undiffer-entiated seronegative polyarthritis	17	1 (lost in FU)	CRP 140 mg/L; neg RF and ACPA	CRP < 2.9 mg/L,	Oral GC	No	-	Complete	NA	NA
22	29	F	No	1st dose, BNT162b2	Undiffer-entiated seronegative monoarthritis (knee)	21	6	CRP<2.9	-	Oral NSAID	No	-	Complete	Yes	Yes
23	67	M	No	2nd dose, BNT162b2	RPm	15	8	CRP 29.4 mg/L; neg RF and ANA	CRP < 2.9 mg/L	Oral GC	No	-	Partial (stiffness and arthralgias)	No	Yes
24	74	F	Dermato-myositis	2nd dose, BNT162b2	RPm	20	9	CRP 87 mg/L, ESR 104 mg/L	CRP 5.9 mg/L, ESR 40 mm/h	Oral GC	Symptoms relapse after GC withdrawal	-	Complete	Yes	Yes

RD flare	Age (years)	sex	Pre-existing autoimmune disease	Dose and Type of vaccine received	Rheumatic AEFI developed	Time to AEFI (days)	Months of FU	Lab exams at diagnosis	Lab exams at last FU visit	First line therapy	Complic-ations after therapy de-escalation	Second line therapy	Clinical response at last FU evaluation	Therapy withdrawal at last FU	Completion of primary vaccination course (3 doses)
25	84	F	Giant cell arteritis	2nd dose, BNT162b	LVV (Aortitis)	15	12	CRP 200 mg/L	CRP < 2.9 mg/L	Iv and oral GC	No	--	Complete	Yes	Yes
26	71	F	Psoriatic a rthritis	1st dose, BNT162b	wrist arthritis	2	12	neg RF and ANA	CRP < 2.9 mg/L	Intra-articular GC injection	No	-	Partial (arthralgias)	Yes	Yes
27	57	F	AOSD	1st dose, BNT162b	Fever, arthralgias and sore throat	15	9	CRP 345 mg/L, Ferritin 813 ug/L	CRP < 2.9, Ferritin 87 ug/L	Oral GC+ anti-IL1	No	-	Complete	No	Yes
28	63	F	RA	2nd dose, BNT162b	PIP joints arthritis of the hands	10	9	CRP < 2.9 mg/L	CRP <2 .9 mg/L	Oral GC	No	-	Complete	No	Yes
29	19	M	SLE	1st dose, BNT162b	Lupus nephritis	30	9	24h proteinuria 1.16 g	24 h proteinuria 2.5g	Oral GC	No	Belimumab + Rituximab	Absent	No	No
30	31	F	UCTD	2nd dose, BNT162b	Poly-arthritis	2	8	CRP < 2.9 mg/L	CRP < 2.9 mg/L	Oral GC	No	-	Complete	Yes	Yes

* after second-line therapy

F: female; M: male; RD: rheumatic disease; AEFI: adverse event following immunisation; FU: follow-up; GC: glucocorticoid; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor; ACPA: anti-citrulline antibodies; NSAID: non-steroidal anti-inflammatory drug; AOSD: adult onset Still disease; MAS: macrophage activation syndrome; RPm: rheumatic polymyalgia; RA: rheumatoid arthritis; PIP: proximal interphalangeal; ANA: anti-nuclear antibodies; Anti-ENA: anti-extractable nuclear antibodies; MSA: myositis specific autoantibodies; LVV: large-vessel vasculitis; SAA: serum amyloid A; SLE: systemic lupus erythematosus; UCTD: undifferentiated connective tissue disease; NA: not available; neg: negative.

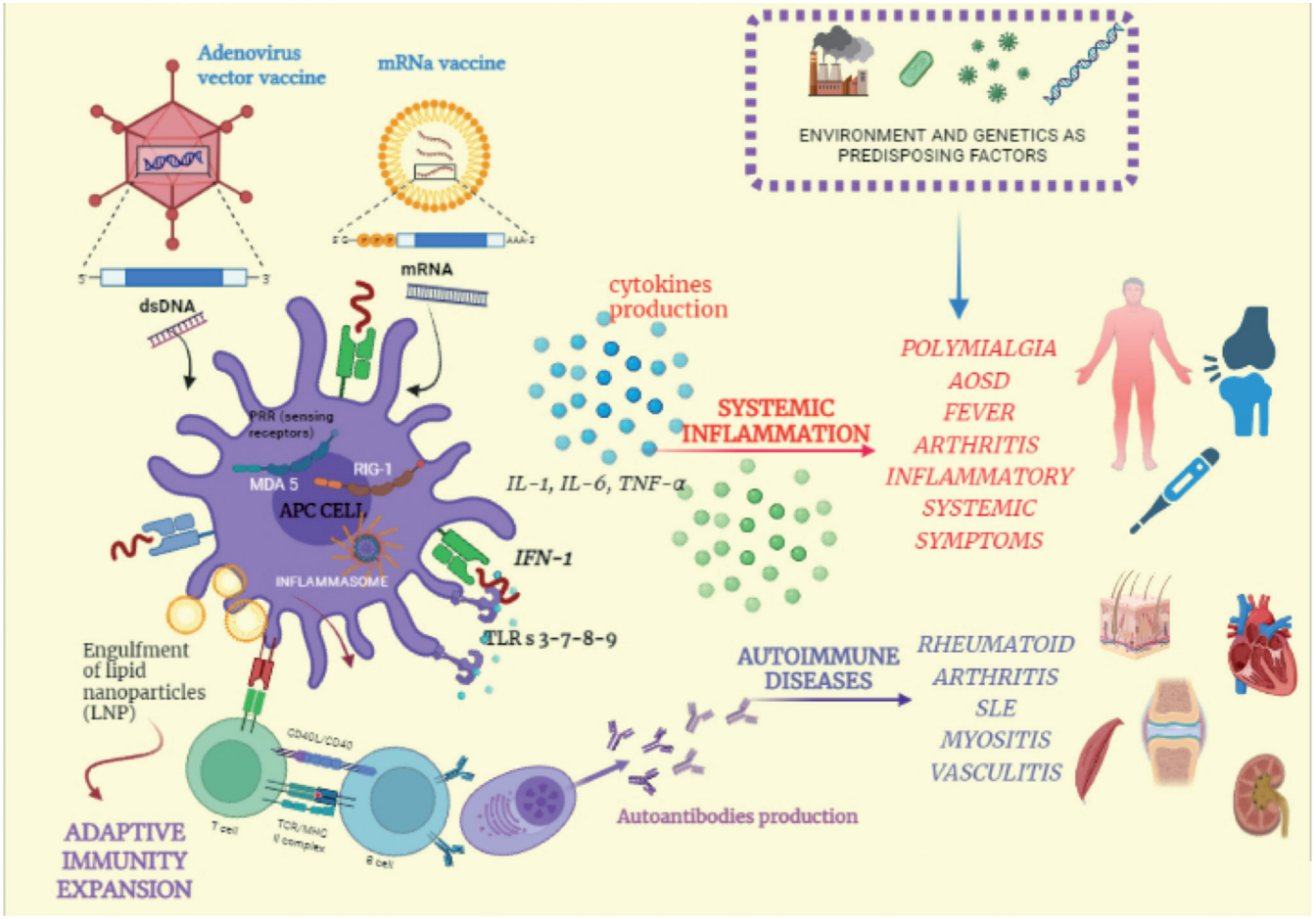

Fig. 2. How SARS-CoV2 vaccine may elicit auto-inflammation.
SARS-COV-2 DNA/mRNA vaccines formulation may activate the innate immune response through Toll-like receptors (TLR), sensing receptors and the inflammasome. In those genetically predisposed (and/or if environmental factors interfere) it is plausible an imbalance of pro-inflammatory cytokines, which may lead to the onset of typical inflammatory symptoms. In addition, lipid nanoparticles function as adjuvant and once engulfed by dendritic cells, both innate and adaptive immunity may expand provoking inflammation and the occurrence of autoantibodies.
AOSD: adult-onset Still's disease; IFN-1: interferon-1; IL: interleukin; DNA: deoxyribonucleic acid; LNP: lipid nanoparticles; MDA-5: melanoma differentiation-associated antigen 5; MHC: major histocompatibility complex; mRNA: micro-ribonucleic acid; PRR: pattern recognition receptors; RIG: retinoic acid-inducible gene; SLE: systemic lupus erythematosus; TNF-α: tumour-necrosis factor alpha; TLR: toll-like receptor.

unleashed according to the different adjuvant type coupled with the vaccine. In this regard, Yokose *et al*. (12) report an increased incidence of gout attacks after receiving the new recombinant zoster vaccine, potentially through a shared pathogenetic mechanism involving NLRP3 inflammasome. Similarly, it has been shown that mRNA vaccines stimulate the innate immunity through the activation of the same endosolic and cytoplasmic nucleic acids receptors (*i.e*. Toll-like receptors) which are also overexpressed by peripheral mononuclear cells in patients with RPm: this would justify the sum of RPm cases following anti-COVID-19 vaccination so far reported in the literature (13). In addition, the BNT162b2 vaccine can elicit an interferon-γ mediated T-helper1 response which is the predominant pathogenetic pathway in patients with AOSD (14) (Fig. 2). However, the exact mechanism exerted by anti-SARS-CoV2 vaccines on the immune system requires further studies to define whether in susceptible patients they could induce the development of autoinflammatory rather than autoimmunity conditions (15) (Fig. 2).
To the best of our knowledge, there are no other published reports showing extensive description of FU data. Our results depict an optimistic scenario in view of the low number of cases and the excellent response to therapy.
Vaccination remains a milestone against infections and its benefits far outweigh the risk of immune side effects even in patients with autoimmune or autoinflammatory disorders. Current recommendations from international rheumatologic societies strongly advise anti-COVID-19 vaccination in patients with RD, with appropriate timing according to disease activity and category of ongoing immunosuppressive therapy.

Conclusions

According to our case series, the RDs following SARS-CoV2 vaccination are generally mild. Short-term FU data are reassuring, suggesting a benign course with prompt response to therapy.
Finally, we observed a strong prevalence of inflammatory conditions that may be directly related to the interaction between vaccine and the immune system.

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